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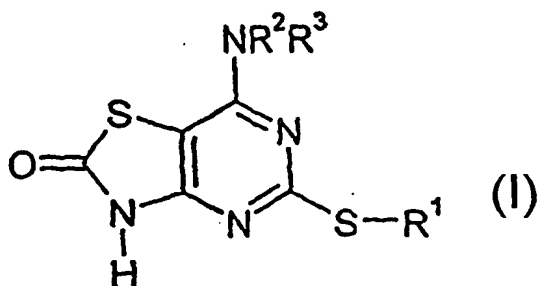
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(54) Title: NOVEL THIAZOLO(4,5-D)PYRIMIDINE COMPOUNDS



(57) Abstract: The invention provides certain thiazolopyrimidine compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof; processes and intermediates used in their preparation, pharmaceutical compositions containing them and their use in therapy.

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**NOVEL THIAZOLO (4,5-D) PYRIMIDINE COMPOUNDS**  
**NOVEL COMPOUNDS**

5 The present invention relates to certain thiazolopyrimidinone compounds, processes and intermediates used in their preparation, pharmaceutical compositions containing them and their use in therapy.

10 WO 98/08847 and EP0778277 each disclose a series of 6,5-hetero bicyclic compounds said to be useful as CRF antagonists.

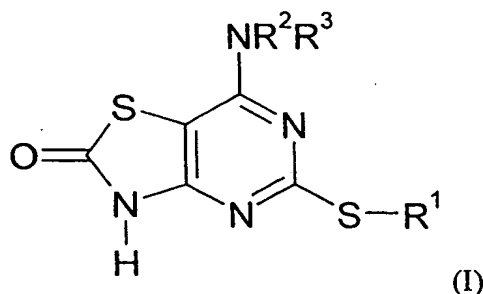
Chemokines play an important role in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted  
15 molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. The chemokine superfamily can be divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C) and Cys-Cys (C-C) families. These are distinguished on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues and sequence similarity.

20 The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

25 The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1 $\alpha$  and 1 $\beta$  (MIP-1 $\alpha$  and MIP-1 $\beta$ ).

30 Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3, CXCR4 and CX3CR1. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

In accordance with the present invention, there is therefore provided a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof:



in which

R¹ represents a C₃-C₇ carbocyclic, C₁-C₈ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl group, each of the groups being optionally substituted by one or more substituent groups independently selected from halogen atoms, -OR⁴, -NR⁵R⁶, -CONR⁵R⁶, -COOR⁷, -NR⁸COR⁹, -SR¹⁰, -SO₂R¹⁰, -SO₂NR⁵R⁶, -NR⁸SO₂R⁹ or an aryl or heteroaryl group, both of which may be optionally substituted by one or more substituents independently selected from halogen atoms, cyano, nitro, -OR⁴, -NR⁵R⁶, -CONR⁵R⁶, -COOR⁷, -NR⁸COR⁹, -SR¹⁰, -SO₂R¹⁰, -SO₂NR⁵R⁶, -NR⁸SO₂R⁹, C₁-C₆ alkyl or trifluoromethyl groups;

R² and R³ each independently represent a hydrogen atom, or a C₃-C₇ carbocyclic, C₁-C₈ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl group, the latter four groups may be optionally substituted by one or more substituent groups independently selected from:

- (a) halogen atoms, -OR⁴, -NR⁵R⁶, -CONR⁵R⁶, -COOR⁷, -NR⁸COR⁹, -SR¹⁰, -SO₂R¹⁰, -SO₂NR⁵R⁶, -NR⁸SO₂R⁹;
- (b) a 3-8 membered ring optionally containing one or more atoms selected from O, S, NR⁸ and itself optionally substituted by C₁-C₃-alkyl or halogen; or
- (c) an aryl group or heteroaryl group each of which may be optionally substituted by one or more substituents independently selected from halogen atoms, cyano, nitro, -OR⁴, -NR⁵R⁶, -CONR⁵R⁶, -NR⁸COR⁹, -SO₂NR⁵R⁶, -NR⁸SO₂R⁹, C₁-C₆ alkyl and trifluoromethyl groups;

R<sup>4</sup> represents hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl or a phenyl group the latter two of which may be optionally substituted by one or more substituent groups independently selected from halogen atoms, phenyl, -OR<sup>11</sup> and -NR<sup>12</sup>R<sup>13</sup>

- 5 R<sup>5</sup> and R<sup>6</sup> independently represent a hydrogen atom or a C<sub>1</sub>-C<sub>6</sub> alkyl or phenyl group the latter two of which may be optionally substituted by one or more substituent groups independently selected from halogen atoms, phenyl, -OR<sup>14</sup> and -NR<sup>15</sup>R<sup>16</sup>, -CONR<sup>15</sup>R<sup>16</sup>, -NR<sup>15</sup>COR<sup>16</sup>, -SONR<sup>15</sup>R<sup>16</sup>, NR<sup>15</sup>SO<sub>2</sub>R<sup>16</sup>
- or
- 10 R<sup>5</sup> and R<sup>6</sup> together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring system optionally containing a further heteroatom selected from oxygen and nitrogen atoms, which ring system may be optionally substituted by one or more substituent groups independently selected from phenyl, -OR<sup>14</sup>, -COOR<sup>14</sup>, -NR<sup>15</sup>R<sup>16</sup>, -CONR<sup>15</sup>R<sup>16</sup>, -NR<sup>15</sup>COR<sup>16</sup>, -SONR<sup>15</sup>R<sup>16</sup>, NR<sup>15</sup>SO<sub>2</sub>R<sup>16</sup> or C<sub>1</sub>-C<sub>6</sub> alkyl, itself
- 15 optionally substituted by one or more substituents independently selected from halogen atoms and -NR<sup>15</sup>R<sup>16</sup> and -OR<sup>17</sup> groups;

- R<sup>10</sup> represents a hydrogen atom or a C<sub>1</sub>-C<sub>6</sub>-alkyl or a phenyl group, the latter two of which may be optionally substituted by one or more substituent groups independently selected
- 20 from halogen atoms, phenyl, -OR<sup>17</sup> and -NR<sup>15</sup>R<sup>16</sup>; and

each of R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup> independently represents a hydrogen atom or a C<sub>1</sub>-C<sub>6</sub>, alkyl, or a phenyl group.

- 25 In the context of the present specification, unless otherwise indicated, an alkyl or alkenyl group or an alkyl or alkenyl moiety in a substituent group may be linear or branched. Aryl groups include phenyl and naphthyl. Heteroaryl groups include 5- or 6-membered aromatic rings containing one or more heteroatoms selected from N, S, O. Examples include pyridine, pyrimidine, thiazole, oxazole, pyrazole, imidazole, furan.

- 30 Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

In formula (I) above, the group  $R^1$  represents a  $C_3$ - $C_7$  carbocyclic,  $C_1$ - $C_8$  alkyl,  $C_2$ - $C_6$  alkenyl or  $C_2$ - $C_6$  alkynyl group, each of the groups being optionally substituted by one or more substituent groups independently selected from halogen atoms,  $-OR^4$ ,  $-NR^5R^6$ ,  $-CONR^5R^6$ ,  $-COOR^7$ ,  $-NR^8COR^9$ ,  $-SR^{10}$ ,  $-SO_2R^{10}$ ,  $-SO_2NR^5R^6$ ,  $-NR^8SO_2R^9$  or an aryl or heteroaryl group, both of which may be optionally substituted by one or more substituents independently selected from halogen atoms, cyano, nitro,  $-OR^4$ ,  $-NR^5R^6$ ,  $-CONR^5R^6$ ,  $-COOR^7$ ,  $-NR^8COR^9$ ,  $-SR^{10}$ ,  $-SO_2R^{10}$ ,  $-SO_2NR^5R^6$ ,  $-NR^8SO_2R^9$ ,  $C_1$ - $C_6$  alkyl or trifluoromethyl groups. Particularly advantageous compounds of formula (I) are those in which  $R^1$  represents an optionally substituted benzyl group. More preferably  $R^1$  represents benzyl or benzyl substituted by one or more  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy or halogen atoms.

When  $R^2$  and  $R^3$  represent a group substituted by one or more 3-8 membered rings optionally containing one or more atoms selected from O, S or  $NR^8$ , examples of such groups include piperidine, pyrrolidine, piperazine and morpholine.

Preferably one of  $R^2$  and  $R^3$  is hydrogen and the other is  $C_1$ - $C_8$  alkyl substituted by hydroxy and one or more methyl or ethyl groups. More preferably one of  $R^2$  and  $R^3$  is hydrogen and the other is  $CH(CH_3)CH_2OH$ ,  $CH(Et)CH_2OH$ ,  $C(CH_3)_2CH_2OH$  or  $CH(CH_2OH)_2$ . When one of  $R^2$  and  $R^3$  is hydrogen and the other is  $CH(CH_3)CH_2OH$  or  $CH(Et)CH_2OH$  the resulting compounds of formula (I) are preferably in the form of the (R) isomer.

Particularly preferred compounds of the invention include:

7-[(2-Hydroxy-1,1-dimethylethyl)amino]-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

(*R*)-7-[[1-(Hydroxymethyl)propyl]amino]-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

(*R*)-7-[(2-Hydroxy-1-methylethyl)amino]-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

5-[[[(2,3-Difluorophenyl)methyl]thio]-7-[(2-hydroxy-1,1-dimethylethyl)amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

5-[[[(2,3-Difluorophenyl)methyl]thio]-7-[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

5-[[[(2,3-difluorophenyl)methyl]thio]-7-[[2-(hydroxyethoxy)ethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

5-[[[(2,3-difluorophenyl)methyl]thio]-7-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]  
thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

7-[(2-aminoethyl)amino]-5-[[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-  
2(3*H*)-one,

5 5-[[[(2,3-difluorophenyl)methyl]thio]-7-[(2-hydroxyethyl)amino]thiazolo[4,5-*d*]pyrimidin-  
2(3*H*)-one,

*N*-[2-[[5-[[[(2,3-difluorophenyl)methyl]thio]-2,3-dihydro-2-oxothiazolo[4,5-*d*]pyrimidin-7-  
yl]amino]ethyl]methanesulfonamide,

(+/-)-5-[[[(2,3-difluorophenyl)methyl]thio]-7-[[2-(2-hydroxyethoxy)-1-

10 methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

7-[[[(1*R*)-2-amino-1-methylethyl]amino]-5-[[[(2,3-difluorophenyl)methyl]thio] thiazolo[4,5-  
*d*]pyrimidin-2(3*H*)-one,

5-[[[(2,3-difluorophenyl)methyl]thio]-7-[[[(1*R*)-2-[(2-hydroxyethyl)amino]-1-  
methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

15 5-[[[(2,3-difluorophenyl)methyl]thio]-7-[[[(1*R*)-2-(dimethylamino)-1-  
methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

5-[[[4-(2-aminoethoxy)-3-chlorophenyl]methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-  
methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

5-[[3-Chloro-4-methoxyphenyl]methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-

20 methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

5-[[[3-Chloro-2-fluorophenyl]methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]  
thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

5-[[[(2,3-Difluorophenyl)methyl]thio]-7-[[[(3*R*,4*R*)-4-hydroxypyrrolidin-3-yl]amino]-  
thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

25 5-[[[(2,3-Difluorophenyl)methyl]thio]-7-[(3*R*)-pyrrolidin-3-ylamino]thiazolo[4,5-  
*d*]pyrimidin-2(3*H*)-one,

7-[[[(1*R*)-2-Hydroxy-1-methylethyl]amino]-5-[[[(2-methyl-4-thiazolyl)methyl]thio]  
thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

7-[[2-Hydroxy-1-(hydroxymethyl)ethyl]amino]-5-[[[(2-methyl-4-thiazolyl)methyl]

30 thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

7-[(2-Hydroxy-1,1-dimethylethyl)amino]-5-[[[(2-methyl-4-thiazolyl)methyl]thio]  
thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

7-[(2-Hydroxy-1,1-dimethylethyl)amino]-5-[[[(2-methylphenyl)methyl]thio] thiazolo[4,5-  
*d*]pyrimidin-2(3*H*)-one,

5 5-[(2-Furanylmethyl)thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-  
*d*]pyrimidin-2(3*H*)-one,

7-[[[(1*R*)-2-Amino-1-methylethyl]amino]-5-[[[(3-chloro-2-fluorophenyl)methyl]thio]  
thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

(2*S*)-2-[[5-[[[(2,3-Difluorophenyl)methyl]thio]-2,3-dihydro-2-oxothiazolo[4,5-*d*]pyrimidin-  
10 7-yl]amino]-3-hydroxy-propanamide,

7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]-5-[(2-thienylmethyl)thio]thiazolo[4,5-  
*d*]pyrimidin-2(3*H*)-one,

7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]-5-[[[3-methyl-4-  
(methylsulfonyl)phenyl]methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

15 5-[[[3-chloro-4-(trifluoromethoxy)phenyl]methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-  
methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

5-[[[2-fluoro-3-(trifluoromethyl)phenyl]methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-  
methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

5-[[[(2,3-difluorophenyl)methyl]thio]-7-[2-[(dimethylamino)ethyl]amino]thiazolo[4,5-  
20 *d*]pyrimidin-2(3*H*)-one,

5-[[[(2-fluorophenyl)methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino] thiazolo[4,5-  
*d*]pyrimidin-2(3*H*)-one,

7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]-5-[[[(2-methoxyphenyl)methyl]thio]  
thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

25 7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]-5-[(2-phenoxyethyl)thio]thiazolo[4,5-  
*d*]pyrimidin-2(3*H*)-one,

7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]-5-[[[(3-methylphenyl)methyl]thio] thiazolo[4,5-  
*d*]pyrimidin-2(3*H*)-one,

5-[[[(2-fluoro-3-methylphenyl)methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]  
30 thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

- 5-[[3-chlorophenyl)methyl]thio]-7-[[1*R*]-2-hydroxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
- 5-[[3-bromophenyl)methyl]thio]-7-[[1*R*]-2-hydroxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
- 5 5-[[4-(difluoromethoxy)phenyl)methyl]thio]-7-[[1*R*]-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
- (+/-)-5-[[2,3-difluorophenyl)methyl]thio]-7-[[2-hydroxy-1-(methoxymethyl)ethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
- 7-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
- 10 5-[[2-bromophenyl)methyl]thio]-7-[[1*R*]-2-hydroxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
- 5-[[2,3-Difluorophenyl)methyl]thio]-7-[[1*R*]-2-hydroxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
- 15 5-[[3-Chloro-2-fluorophenyl)methyl]thio]-7-[[1*R*]-2-hydroxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
- (+/-)-5-[[2,3-difluorophenyl)methyl]thio]-7-[[2-hydroxy-1-(methoxymethyl)ethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
- 7-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
- 20 7-[[1*R*]-2-Hydroxy-1-methylethyl]amino]-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
- 5-[(5-chloro-1,2,3-thiadiazol-4-yl)thio]-7-[[1*R*]-2-hydroxy-1-methylethyl]amino]-thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
- 25 and their pharmaceutically acceptable salts and solvates.

Particular salts of compounds of formula (I) include:

- 5-[[2,3-Difluorophenyl)methyl]thio]-7-[[1*R*]-2-hydroxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one sodium salt,
- 30 5-[[3-Chloro-2-fluorophenyl)methyl]thio]-7-[[1*R*]-2-hydroxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one sodium salt,



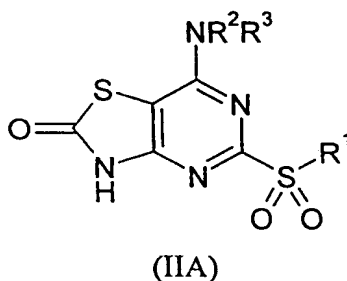
(+/-)-5-[[[(2,3-difluorophenyl)methyl]thio]-7-[[2-hydroxy-1-(methoxymethyl)ethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one sodium salt,  
 7-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one sodium salt, or  
 7-[[[(1*R*)-2-Hydroxy-1-methylethyl]amino]-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one sodium salt.

Further particular salts of compounds of formula (I) include:

7-[[[(1*R*)-2-amino-1-methylethyl]amino]-5-[[[(2,3-difluorophenyl)methyl]thio] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one trifluoroacetate,  
 5-[[[(2,3-difluorophenyl)methyl]thio]-7-[[[(1*R*)-2-[(2-hydroxyethyl)amino]-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one trifluoroacetate,  
 5-[[[(2,3-difluorophenyl)methyl]thio]-7-[[[(1*R*)-2-(dimethylamino)-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,  
 5-[[[4-(2-aminoethoxy)-3-chlorophenyl]methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one trifluoroacetate,  
 5-[[[(2,3-difluorophenyl)methyl]thio]-7-[2-[(dimethylamino)ethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one monohydrochloride, or  
 5-[[[(2,3-Difluorophenyl)methyl]thio]-7-[(3*R*)-pyrrolidin-3-ylamino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one dihydrochloride.

According to the invention there is also provided a process for the preparation of a compound of formula (I) which comprises either:

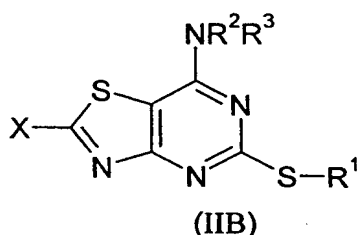
Treatment of a compound of formula (IIA)



where  $R^1$ ,  $R^2$  and  $R^3$  are as defined in formula (I) with a thiol  $R^1SH$  in the presence of a suitable base and optionally forming a pharmaceutically acceptable salt.. The reaction may be carried out in a mixed solvent of DMSO and ethanol at a temperature between  $0^\circ C$  and  $100^\circ C$  using sodium borohydride as the base.

Compounds of formula (IIA) where  $R^1$ ,  $R^2$  and  $R^3$  are as defined in formula (I) may be prepared by treatment of compounds of formula (I) with a suitable oxidising agent such as oxone. The reaction may be carried out in a solvent such as acetonitrile at a temperature between  $0^\circ C$  and  $100^\circ C$ .

Or treatment of a compound of formula (IIB):

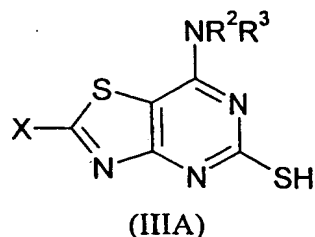


where  $R^1$ ,  $R^2$  and  $R^3$  are as defined in formula (I) and X is a leaving group with a metal alkoxide, followed by treatment with an acid or base and optionally forming a pharmaceutically acceptable salt.

X is any suitable leaving group such as halogen. The reaction may be carried out in an alcohol solvent such as methanol and the deprotection carried out in a solvent such as 1,4-dioxane. Examples of metal alkoxides include potassium methoxide. Examples of suitable acids include hydrochloric acid. Preferably the compound of formula (IIB) is treated with a metal alkoxide such as potassium methoxide followed by an acid such as conc. HCl in a solvent such as 1,4-dioxane.

Compounds of formula (IIB) where  $R^1$ ,  $R^2$  and  $R^3$  are as defined in formula (I) and X is a halogen, may be prepared from corresponding compounds (IIB) where  $R^1$ ,  $R^2$  and  $R^3$  are as defined in formula (I) and X is  $NH_2$  by treatment with a diazotizing agent such as isoamyl nitrite and a halogenating agent such as bromoform.

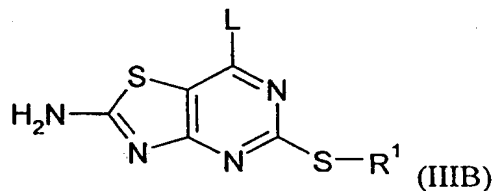
Compounds of formula (IIB) where  $R^1$ ,  $R^2$  and  $R^3$  are as defined in formula (I) and X is  $NH_2$  may be prepared either by treatment of a compound of formula (IIIA):



5 where  $R^2$  and  $R^3$  are as defined in formula (I) and X is  $NH_2$  with a compound of formula  $R^1X$  where  $R^1$  is as defined above and X is a leaving group such as bromide in the presence of a base such as diisopropylethylamine in an inert solvent such as DMSO/*N*-methylpyrrolidinone at a temperature between  $0^\circ C$  and  $100^\circ C$ .

10 Compounds of formula (IIIA) where  $R^2$  and  $R^3$  are as defined in formula (I) and X is  $NH_2$  may be prepared by treatment of a compound of formula (IIB) where  $R^2$  and  $R^3$  are as defined in formula (I), X is  $NH_2$  and  $R^1$  is a suitable benzyl group such as benzyl or 2,3-difluorobenzyl with a reducing medium such as sodium metal in liquid ammonia, or by treatment of a compound of formula (IIIB):

15



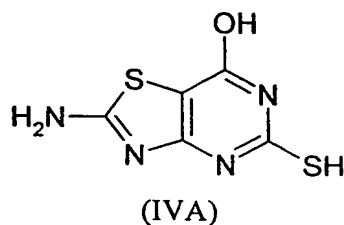
20 where  $R^1$  is as defined in formula (I) and L is a leaving group such as chlorine with an amine  $HNR^2R^3$  where  $R^2$  and  $R^3$  are as defined in formula (I). The reaction may be carried out in a solvent such as *N*-methyl-pyrrolidine at a temperature between  $0^\circ C$  and  $150^\circ C$ .

Compounds of formula (IIIB) where  $R^1$  is as defined in formula (I) and L is a halogen may be prepared by treating a compound of formula (IIIB) where  $R^1$  is as defined in formula (I) and L is a hydroxyl group with a halogenating agent such as phosphorous oxychloride.

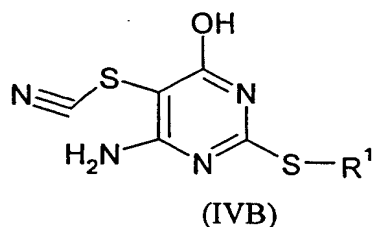
25 The reaction may be carried out in the presence of dimethylaniline at reflux.

Compounds of formula (IIIB) where  $R^1$  is as defined in formula (I) and L is a hydroxyl group may be formed either by treatment of a compound of formula (IVA) with a compound of formula  $R^1X$  where  $R^1$  is as defined above and X is a leaving group such as

bromide in the presence of a base such as potassium *tert*-butoxide in an inert solvent such as DMSO at ambient temperature.

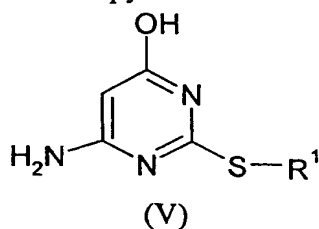


Or by heating a compound of formula (IVB) where R<sup>1</sup> is as defined above.

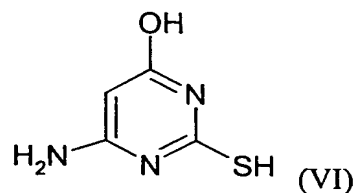


The reaction is preferably carried out in a suitable solvent such as DMF at elevated temperature, for example at about 120°C.

- 15 Compounds of formula (IVB) may be readily prepared by reacting a compound of general formula (V) wherein R<sup>1</sup> is as defined above, with potassium thiocyanate and bromine in an inert solvent such as dimethylformamide/pyridine.



Compounds of formula (V) are suitably prepared by reacting a compound of formula (VI):



with a compound of formula  $R^1X$  where  $R^1$  is as defined above and X is a leaving group such as bromide in the presence of a base such as sodium hydride in an inert solvent such as DMF at ambient temperature.

5 Compounds of formula (IVA) and (VI) are either commercially available or are well known in the literature.

It will be appreciated by those skilled in the art that in the processes described above the functional groups (e.g. hydroxyl groups) of intermediate compounds may need to be  
10 protected by protecting groups. The final stage in the preparation of the compounds of the invention may involve the removal of one or more protecting groups. The protection and deprotection of functional groups is fully described in 'Protective Groups in Organic Chemistry', edited by J. W. F. McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 2nd edition, T. W. Greene & P. G. M. Wuts, Wiley-Interscience  
15 (1991).

Novel intermediate compounds form a further aspect of the invention. In particular compounds of formula (IIA), (IIB) and (IIIA) are novel and form an aspect of the  
20 invention.

The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably a basic addition salt such as sodium, potassium, calcium, aluminium, lithium, magnesium, zinc, benzathine, chloroprocaine, choline, diethanolamine, ethanolamine, ethyldiamine, meglumine, tromethamine or procaine, or an  
25 acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate.

The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of chemokine receptors, and may be used in the treatment (therapeutic or prophylactic) of  
30 conditions/diseases in human and non-human animals which are exacerbated or caused by excessive or unregulated production of chemokines. Examples of such conditions/diseases include:

- (1) **(the respiratory tract)** obstructive airways diseases including chronic  
35 obstructive pulmonary disease (COPD); asthma, such as bronchial, allergic, intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma

(e.g. late asthma and airways hyper-responsiveness); bronchitis; acute, allergic, atrophic rhinitis and chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca and rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous and pseudomembranous rhinitis and scrofulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) and vasomotor rhinitis; sarcoidosis, farmer's lung and related diseases, fibroid lung and idiopathic interstitial pneumonia;

- (2) **(bone and joints)** rheumatoid arthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome and systemic sclerosis;
- (3) **(skin)** psoriasis, atopic dermatitis, contact dermatitis and other eczematous dermatides, seborrhectic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythemas, cutaneous eosinophilias, uveitis, Alopecia areata and vernal conjunctivitis;
- (4) **(gastrointestinal tract)** Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema;
- (5) **(other tissues and systemic disease)** multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus, systemic lupus, erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, sezary syndrome and idiopathic thrombocytopenia pupura; post-operative adhesions, and sepsis.
- (6) **(allograft rejection)** acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease;
- (7) Cancers, especially non-small cell lung cancer (NSCLC), malignant melanoma, prostate cancer and squamous sarcoma, and tumour metastasis;

(8) Diseases in which angiogenesis is associated with raised CXCR2 chemokine levels (e.g. NSCLC, diabetic retinopathy).

(9) Cystic fibrosis, stroke, re-perfusion injury in the heart, brain, peripheral limbs and other organs.

(10) Burn wounds & chronic skin ulcers

(11) Reproductive Diseases (e.g. Disorders of ovulation, menstruation and implantation, Pre-term labour, Endometriosis)

Thus, the present invention provides a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

Preferably the compounds of the invention are used to treat diseases in which the chemokine receptor belongs to the CXC chemokine receptor subfamily, more preferably the target chemokine receptor is the CXCR2 receptor,

Particular conditions which can be treated with the compounds of the invention are psoriasis, diseases in which angiogenesis is associated with raised CXCR2 chemokine levels, and COPD. It is preferred that the compounds of the invention are used to treat psoriasis.

In a further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In a still further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of chemokine receptor activity is beneficial.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

The invention still further provides a method of treating a chemokine mediated disease wherein the chemokine binds to a chemokine (especially CXCR2) receptor, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore  
5 defined.

The invention also provides a method of treating an inflammatory disease, especially psoriasis, in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula  
10 (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

15 The compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier.  
20 Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

25 The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical  
30 composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the lung and/or  
35 airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of



tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally. Preferably the compounds of the invention are administered orally.

5 The invention will now be further illustrated by reference to the following examples. In the examples the Nuclear Magnetic Resonance (NMR) spectra were measured on a Varian Unity Inova 300 or 400 MHz spectrometer and the Mass Spectrometry (MS) spectra measured on a Finnigan Mat SSQ7000 or Micromass Platform spectrometer. Where  
10 necessary, the reactions were performed under an inert atmosphere of either nitrogen or argon. Chromatography was generally performed using Matrex Silica 60<sup>®</sup> (35-70 micron) or Prolabo Silica gel 60<sup>®</sup> (35-70 micron) suitable for flash silica gel chromatography. High pressure liquid chromatography purification was performed using either a Waters Micromass LCZ with a Waters 600 pump controller, Waters 2487 detector and Gilson  
15 FC024 fraction collector or a Waters Delta Prep 4000. The abbreviations m.p. and DMSO used in the examples stand for melting point and dimethyl sulphoxide respectively.

**Example 1****7-[(2-Hydroxy-1,1-dimethylethyl)amino]-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one****(a) Thiocyanic acid, 6-amino-1,4-dihydro-4-oxo-2-[(phenylmethyl)thio]-5-pyrimidinyl ester**

6-Amino-2-[(phenylmethyl)thio]-4(1*H*)-pyrimidinone (10.5g) [preparation as described in WO 9635678] and potassium thiocyanate (25g) in *N,N*-dimethylformamide (200ml) were heated together at 65°C. Pyridine (6.3ml) was added and the solution cooled to 5°C. Bromine (2.2ml) was added slowly and the reaction mixture stirred for 2 hours at 5-10°C. The reaction mixture was poured onto ice water, stirred for 1 hour and the solid was isolated by filtration. After washing with water and ether, a pure sample was obtained after trituration with hot methanol.

MS (APCI) 291 (M+H, 100%).

**(b) 2-Amino-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-7(4*H*)-one**

The product of example 1 step a) (7.35g) was heated at 120°C in *N,N*-dimethylformamide (40ml)/water (10ml) for 10 hours. After cooling, the resulting solid was filtered off, washed with water, then ethyl acetate to give the subtitle compound.

m.p. 325°C

MS (APCI) 291 (M+H, 100%).

**(c) 7-Chloro-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2-amine**

The product from example 1 step b) (0.89g), phosphorus oxychloride (12ml) and *N,N*-dimethylaniline (1.2ml) were heated at reflux for 2 hours. The cooled reaction mixture was poured onto ice water and stirred for 2 hours. Chromatography (SiO<sub>2</sub>, methanol/dichloromethane as eluant) gave the sub-title compound.

m.p. 217-218.5°C

MS (APCI) 309 (M+H, 100%).

**(d) 2-[[2-Amino-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-2-methyl-1-propanol**

5 The product from example 1 step c) (0.6g) and 1-amino-2-methyl-propan-2-ol (1.1g) in tetrahydrofuran (10ml) was heated in a sealed vessel at 100 °C for 18 hours. The mixture was evaporated to dryness and purified (SiO<sub>2</sub>, ethyl acetate as eluant) to give the subtitle compound (0.46g).

10 MS (APCI) 362 (M+H<sup>+</sup>, 100%).

**(e) 2-[[2-Bromo-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-2-methyl-1-propanol**

15 To a solution of the product from example 1 step d) (0.1g) in bromoform (5ml) was added isoamyl nitrite (0.13ml) and the mixture heated at 60°C for 10 mins. The mixture was evaporated to dryness and purified (SiO<sub>2</sub>, ethyl acetate: dichloromethane 1:9 as eluant) to give the subtitle compound as a colourless solid (0.043g).

20 MS (APCI) 427 (M+H<sup>+</sup>, 100%).

**(f) 2-[[2-Methoxy-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-2-methyl-1-propanol**

25 To a solution of the product from example 1 step e) (0.36g) in methanol (5ml) was added potassium hydroxide (0.095g) and the mixture stirred for 30 mins. The mixture was neutralised with concentrated hydrochloric acid then evaporated to dryness and purified (SiO<sub>2</sub>, ethyl acetate: dichloromethane 1:9 as eluant) to give the subtitle compound as a colourless solid (0.245g).

30

MS (APCI) 377 (M+H<sup>+</sup>, 100%).

**(g) 7-[(2-Hydroxy-1,1-dimethylethyl)amino]-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

To a solution of the product from example 1 step f) (0.21g) in 1,4-dioxane (5ml) was added  
5 water (0.1ml) and concentrated hydrochloric acid (1 drop). The mixture heated at 45°C for  
3 hours then evaporated to dryness. Recrystallisation (acetonitrile) gave the title compound  
(0.110g).

M.P 207-8 °C

10 MS (APCI) 363 (M+H<sup>+</sup>, 100%).

NMR δH (*d*<sub>6</sub>-DMSO) 12.37 (1H, s), 7.43-7.23 (5H, m), 6.61 (1H, bs), 4.81 (1H, t), 4.34  
(2H, s), 3.55 (2H, bs), 1.32 (6H, s).

**EXAMPLE 2**

15 **(*R*)-7-[[1-(Hydroxymethyl)propyl]amino]-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

**(a) (*R*)-2-[[2-Amino-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1-  
butanol**

20 To a mixture of the product of example 1 step c) (2.5g) and (*R*)-(-)-2-amino-1-butanol  
(5g) in a solvent of N-methylpyrrolidinone (10 ml) was added *N,N*-diisopropylethylamine  
(5 ml) and the resultant mixture heated at 100°C for 10 hours. The mixture was poured into  
water and the product collected by filtration to give the subtitle compound (2.5g)

25 MS (APCI) 362 (M+H<sup>+</sup>, 100%).

**(b) (*R*)-2-[[2-Bromo-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1-  
butanol**

30 Prepared by the method of example 1 step e), using the product of example 2 step a).

MS (APCI) 427 (M+H<sup>+</sup>, 100%).

(c) *(R)*-2-[[2-Methoxy-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1-butanol

Prepared by the method of example 1 step f), using the product of example 2 step b).

MS (APCI) 377 ( $M+H^+$ , 100%).

(d) *(R)*-7-[[1-(Hydroxymethyl)propyl]amino]-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

Prepared by the method of example 1 step g), using the product of example 2 step c).

M.P 217-8 °C

MS (APCI) 363 ( $M+H^+$ , 100%).

NMR  $\delta$ H (*d*<sub>6</sub>-DMSO) 12.37 (1H, s), 7.43-7.21 (6H, m), 4.68(1H, t), 4.32 (2H, q), 4.09 (1H, bs), 3.47-3.32 (2H, m), 1.69-1.59 (1H, m), 1.48-1.41 (1H, m), 0.82 (3H, t).

### EXAMPLE 3

*(R)*-7-[(2-Hydroxy-1-methylethyl)amino]-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

(a) *(R)*-2-[[2-Amino-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]- 1-propanol

Prepared by the method of example 2 step a), using the product of example 1 step c) and *(R)*-(-)-2-amino-1-propanol.

MS (APCI) 412 ( $M+H^+$ , 100%).

(b) *(R)*-2-[[2-Bromo-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]- 1-propanol

Prepared by the method of example 1 step e), using the product of example 3 step a)

MS (APCI) 348 ( $M+H^+$ , 100%).

**(c) (R)-2-[[2-Methoxy-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1-propanol**

5 Prepared by the method of example 1 step f), using the product of example 3 step b)

MS (APCI) 363 (M+H<sup>+</sup>, 100%).

**(d) (R)-7-[(2-Hydroxy-1-methylethyl)amino]-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

Prepared by the method of example 1 step g), using the product of example 3 step c).

MS (APCI) 349 (M+H<sup>+</sup>, 100%).

15 NMR δH (*d*<sub>6</sub>-DMSO) 12.38 (1H, s), 7.44-7.20 (6H, m), 4.72 (1H, t), 4.32 (2H, m), 4.23 (1H, m), 3.49-3.29 (2H, m), 1.11(3H, d).

**EXAMPLE 4**

**5-[[[(2,3-Difluorophenyl)methyl]thio]-7-[(2-hydroxy-1,1-dimethylethyl)amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

**(a) 2-Amino-5-[[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7(4*H*)-one**

25 Potassium *t*-butoxide solution (0.45ml of 1M solution in tetrahydrofuran) was added to a stirred solution of 2-amino-5,6-dihydro-5-thioxo-thiazolo[4,5-*d*]pyrimidin-7(4*H*)-one (0.09g) [Cited: Indian J. Chem., Sect. B (1989), 28B(11), 964-5.] and 2,3-difluorobenzyl bromide in dimethyl sulphoxide (2ml). After stirring for 3 days, the reaction mixture was poured onto water to give and the subtitle compound, isolated by filtration.

30 MS (APCI) 327 (M+H<sup>+</sup>, 100%).

**(b) 7-Chloro-5-[[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-2-amine**

Prepared by the method of example 1 step c), using the product of example 4 step a).

35

MS (APCI) 345 (M+H<sup>+</sup>, 100%).

**(c) 2-[[2-Amino-5-[[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-2-methyl-1-propanol**

- 5 Prepared by the method of example 2 step a), using the product of example 4, step b) and 2-amino-2-methylpropanol.

MS (APCI) 398 (M+H<sup>+</sup>, 100%).

10 **(d) 2-[[2-Bromo-5-[[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-2-methyl-1-propanol**

Prepared by the method of example 1 step e), using the product of example 4 step c).

- 15 MS (APCI) 462 (M+H<sup>+</sup>, 100%).

**(e) 2-[[5-[[[(2,3-Difluorophenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]-2-methyl-1-propanol**

Prepared by the method of example 1 step f), using the product of example 4 step d).

- 20 MS (APCI) 413 (M+H<sup>+</sup>, 100%).

**(f) 5-[[[(2,3-Difluorophenyl)methyl]thio]-7-[(2-hydroxy-1,1-dimethylethyl)amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

Prepared by the method of example 1 step f), using the product of example 4 step e).

MS (APCI) 399 (M+H<sup>+</sup>, 100%).

- 25 NMR  $\delta$ H (*d*<sub>6</sub>-DMSO) 12.41 (1H, s), 7.41-7.30 (2H, m), 7.21-7.13 (1H, m), 6.64 (1H, bs), 4.79 (1H, t), 4.41 (2H, s), 3.53 (2H, d), 1.29 (6H, s).

**EXAMPLE 5**

**5-[[[(2,3-Difluorophenyl)methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

- 5    **(a) (2*R*)-2-[[2-Amino-5-[[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1-propanol**

Prepared by the method of example 2 step a), using the product of example 4 step b) and (*R*)-(-)-2-amino-1-propanol.

10

MS (APCI) 384 ( $M+H^+$ , 100%).

**(b) (2*R*)-2-[[2-Bromo-5-[[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1-propanol**

15

Prepared by the method of example 1 step e), using the product of example 5 step a).

MS (APCI) 448 ( $M+H^+$ , 100%).

- 20    **(c) (2*R*)-2-[[5-[[[(2,3-difluorophenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1-propanol**

Prepared by the method of example 1 step f), using the product of example 5 step b)

- 25    MS (APCI) 398 ( $M+H^+$ , 100%).

**(d) 5-[[[(2,3-Difluorophenyl)methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

- 30    Prepared by the method of example 1 step g), using the product of example 5 step c).

MS (APCI) 385 ( $M+H^+$ , 100%).

NMR  $\delta$ H ( $d_6$ -DMSO) 12.41 (1H, s), 7.41-7.11 (4H, m), 4.72 (1H, t), 4.39 (2H, m), 4.21 (1H, m), 3.47-3.29 (2H, m), 1.09 (3H, d).

35



**EXAMPLE 6**

5-[[2,3-difluorophenyl)methyl]thio]-7-[[2-(hydroxyethoxy)ethyl]amino]thiazolo[4,5-  
*d*]pyrimidin-2(3*H*)-one

5  
(a) 2-[2-[[2-amino-5-[[2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-  
yl]amino]ethoxy]ethanol,

Prepared by the method of example 2 step a), using the product of example 4, step b) and  
10 2-(2-aminoethoxy)-ethanol.

MS (APCI) 414 (M+H<sup>+</sup>, 100%).

15 (b) 2-[2-[[2-bromo-5-[[2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-  
yl]amino]ethoxy]ethanol,

Prepared by the method of example 1 step e), using the product of example 6 step a).

MS (APCI) 478 (M+H<sup>+</sup>, 100%).

20 (c) 2-[2-[[5-[[2,3-difluorophenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-  
yl]amino]ethoxy]ethanol,

Prepared by the method of example 1 step f), using the product of example 6 step b).

25 MS (APCI) 429 (M+H<sup>+</sup>, 100%).

(d) 5-[[2,3-difluorophenyl)methyl]thio]-7-[[2-(2-hydroxyethoxy)ethyl]amino]  
thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

30 Prepared by the method of example 1 step g), using the product of example 6 step c).

M.P 213-4 °C

MS (APCI) 415 (M+H<sup>+</sup>, 100%).

35 NMR δH (*d*<sub>6</sub>-DMSO) 12.41 (1H, s), 7.39-7.11 (4H, m), 4.57 (1H, t), 4.39 (2H, s), 3.57-  
3.38 (8H, m).

**EXAMPLE 7**

**5-[[[(2,3-difluorophenyl)methyl]thio]-7-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,**

**(a) 2-[[[2-amino-5-[[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1,3-propanediol,**

Prepared by the method of example 2 step a), using the product of example 4, step b) and 2-amino-1,3-propanediol.

MS (APCI) 400 ( $M+H^+$ , 100%).

**(b) 2-[[[2-Bromo-5-[[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1,3-propanediol,**

Prepared by the method of example 1 step e), using the product of example 7 step a).

MS (APCI) 464 ( $M+H^+$ , 100%).

**(c) 2-[[[5-[[[(2,3-difluorophenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1,3-propanediol,**

Prepared by the method of example 1 step f), using the product of example 7 step b).

MS (APCI) 415 ( $M+H^+$ , 100%).

**d) 5-[[[(2,3-difluorophenyl)methyl]thio]-7-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,**

Prepared by the method of example 1 step g), using the product of example 7 step c).

M.P 178-9°C

MS (APCI) 401 ( $M+H^+$ , 100%).

NMR  $\delta$ H ( $d_6$ -DMSO) 12.41 (1H, s), 7.42-7.11 (4H, m), 4.66 (2H, s), 4.40 (2H, s), 4.19 (1H, m), 3.49 (4H, m).

**EXAMPLE 8**

**7-[(2-aminoethyl)amino]-5-[[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,**

**(a) [2-[[2-amino-5-[[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]ethyl]-carbamic acid, 1,1-dimethylethyl ester**

Prepared by the method of example 2 step a), using the product of example 4, step b) and (2-aminoethyl)-carbamic acid, 1,1-dimethylethyl ester.

MS (APCI) 469 ( $M+H^+$ , 100%).

**b) [2-[[2-bromo-5-[[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]ethyl]-carbamic acid, 1,1-dimethylethyl ester**

Prepared by the method of example 1 step e), using the product of example 8 step a).

MS (APCI) 533 ( $M+H^+$ , 100%).

**c) [2-[[5-[[[(2,3-difluorophenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]ethyl]-carbamic acid, 1,1-dimethylethyl ester**

Prepared by the method of example 1 step f), using the product of example 8 step b).

MS (APCI) 489 ( $M+H^+$ , 100%).

**d) 7-[(2-aminoethyl)amino]-5-[[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,**

Prepared by the method of example 1 step g), using the product of example 8 step c).

M.P 215-6 °C

MS (APCI) 370 ( $M+H^+$ , 100%).

NMR  $\delta$ H (*d*<sub>6</sub>-DMSO) 12.00 (1H, s), 7.45-7.11 (3H, m), 6.35 (1H, bs), 4.37 (2H, s), 3.48 (2H, m), 2.92 (2H, t),

**EXAMPLE 9**

**5-[[[(2,3-difluorophenyl)methyl]thio]-7-[(2-hydroxyethyl)amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,**

**(a) 2-[[[2-amino-5-[[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]ethanol,**

Prepared by the method of example 2 step a), using the product of example 4, step b) and ethanolamine

MS (APCI) 370 (M+H<sup>+</sup>, 100%).

**(b) 2-[[[2-bromo-5-[[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]ethanol,**

Prepared by the method of example 1 step e), using the product of example 9 step a).

MS (APCI) 434 (M+H<sup>+</sup>, 100%).

**c) 2-[[[5-[[[(2,3-difluorophenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]ethanol,**

Prepared by the method of example 1 step f), using the product of example 9 step b).

MS (APCI) 385 (M+H<sup>+</sup>, 100%).

**d) 5-[[[(2,3-difluorophenyl)methyl]thio]-7-[(2-hydroxyethyl)amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,**

Prepared by the method of example 1 step g), using the product of example 9 step c).

M.P 217-9 °C

MS (APCI) 371 (M+H<sup>+</sup>, 100%).

NMR δ<sub>H</sub> (δ<sub>6</sub>-DMSO) 12.43 (1H, s), 7.67-7.64 (1H, m), 7.39-7.33 (2H, m), 7.16-7.12 (1H, m), 4.73 (1H, t), 4.40 (2H, s), 3.52-3.42 (4H, m).

**EXAMPLE 10**

***N*-[2-[[5-[[2,3-difluorophenyl)methyl]thio]-2,3-dihydro-2-oxothiazolo[4,5-*d*]pyrimidin-7-yl]amino]ethyl]methanesulfonamide,**

**(a) *N*-[2-[[2-amino-5-[[2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]ethyl]methanesulfonamide,**

Prepared by the method of example 2 step a), using the product of example 4, step b) and  
*N*-[2-aminoethyl]-methanesulfonamide,  
MS (APCI) 448 (M+H<sup>+</sup>, 100%).

**b) *N*-[2-[[2-bromo-5-[[2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]ethyl]methanesulfonamide,**

Prepared by the method of example 1 step e), using the product of example 10 step a).

MS (APCI) 511 (M+H<sup>+</sup>, 100%).

**c) *N*-[2-[[5-[[2,3-difluorophenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]ethyl]methanesulfonamide,**

Prepared by the method of example 1 step f), using the product of example 10 step b).

MS (APCI) 462 (M+H<sup>+</sup>, 100%).

**d) *N*-[2-[[5-[[2,3-difluorophenyl)methyl]thio]-2,3-dihydro-2-oxothiazolo[4,5-*d*]pyrimidin-7-yl]amino]ethyl]methanesulfonamide,**

Prepared by the method of example 1 step g), using the product of example 10 step c).

M.P 225-6 °C

MS (APCI) 448 (M+H<sup>+</sup>, 100%).

NMR δH (*d*<sub>6</sub>-DMSO) 12.49 (1H, s), 7.72 (1H, t), 7.41-7.13 (4H, m), 4.43 (2H, bs), 3.49 (2H, m), 3.13 (2H, m), 2.89 (3H, s).

**EXAMPLE 11**

**(+/-)-5-[[[(2,3-difluorophenyl)methyl]thio]-7-[[2-(2-hydroxyethoxy)-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,**

- 5 **(a) (+/-)-2-[2-[[2-amino-5-[[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]propoxy]ethanol,**

Prepared by the method of example 2 step a), using the product of example 4, step b) and (+/-)-2-[2-aminopropoxy]ethanol,

10

MS (APCI) 428 (M+H<sup>+</sup>, 100%).

- b) (+/-)-2-[2-[[2-bromo-5-[[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]propoxy]ethanol,**

15

Prepared by the method of example 1 step e), using the product of example 11 step a).

MS (APCI) 492 (M+H<sup>+</sup>, 100%).

- 20 **c) (+/-)-2-[2-[[5-[[[(2,3-difluorophenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]propoxy]ethanol,**

Prepared by the method of example 1 step f), using the product of example 11 step b).

- 25 MS (APCI) 443 (M+H<sup>+</sup>, 100%).

- d) (+/-)-5-[[[(2,3-difluorophenyl)methyl]thio]-7-[[2-(2-hydroxyethoxy)-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,**

- 30 Prepared by the method of example 1 step g), using the product of example 11 step c).

M.P 221-2 °C

MS (APCI) 429 (M+H<sup>+</sup>, 100%).

NMR δH (*d*<sub>6</sub>-DMSO) 12.43 (1H, s), 7.47-7.30 (3H, m), 7.17-7.13 (1H, m), 4.56 (1H, t),

- 35 4.40 (2H, s), 4.35 (1H, m), 3.49-3.32 (6H, m), 1.10 (3H, d).

**EXAMPLE 12**

**7-[[[(1*R*)-2-amino-1-methylethyl]amino]-5-[[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one trifluoroacetate,**

- 5 **(a) (2*R*)-2-[[2-amino-5-[[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]propanamide,**

Prepared by the method of example 2 step a), using the product of example 4, step b) and (2*R*)-2-amino-propanamide hydrochloride,

10

MS (APCI) 397 ( $M+H^+$ , 100%).

- (b) *N*<sup>7</sup>-[(1*R*)-2-amino-1-methylethyl]-5-[[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidine-2,7-diamine**

15

To a solution of the product from example 12 step a) (0.3 g) in dry tetrahydrofuran (10 ml) was added 2M borane in THF (10 ml) and the mixture heated under reflux for 6 hours. Quenched while hot with methanol (30 ml), evaporated to dryness and the residue taken up into methanol (30 ml) containing a few drops of concentrated hydrochloric acid. The mixture was then heated under reflux for a further 1 hour, evaporated to dryness to give a pale yellow solid.

20

MS (APCI) 383 ( $M+H^+$ , 100%).

- 25 **(c) [(2*R*)-2-[[2-amino-5-[[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]propyl]carbamic acid, 1,1-dimethylethyl ester**

To a solution of the product from example 12 step b) (1.6 g) in THF (50 ml) was added di-tert-butylidicarbonate (0.91 g) and the mixture stirred for 2 days. Evaporated to dryness to give 2.0 g.

30

MS (APCI) 483 ( $M+H^+$ , 100%).

- (d) [(2*R*)-2-[[2-bromo-5-[[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]propyl]carbamic acid, 1,1-dimethylethyl ester**

35

Prepared by the method of example 1 step e), using the product of example 12 step c).

MS (APCI) 547 ( $M+H^+$ , 100%).

5 (e) [(2*R*)-2-[[5-[[[(2,3-difluorophenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]propyl]carbamic acid, 1,1-dimethylethyl ester

Prepared by the method of example 1 step f), using the product of example 12 step d).

10 MS (APCI) 498 ( $M+H^+$ , 100%).

(f) 7-[[[(1*R*)-2-amino-1-methylethyl]amino]-5-[[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one trifluoroacetate,

15 Prepared by the method of example 1 step g), using the product of example 12 step e) and purified by the method of example 15 step f).

MS (APCI) 384 ( $M+H^+$ , 100%).

20 NMR  $\delta$ H ( $d_6$ -DMSO) 12.55 (1H, s), 7.81 (3H, bs), 7.45-7.31 (4H, m), 7.18-7.13 (1H, m), 4.51-4.34 (3H, m), 2.95 (2H, m), 1.14 (3H, d).

### EXAMPLE 13

5-[[[(2,3-difluorophenyl)methyl]thio]-7-[[[(1*R*)-2-[(2-hydroxyethyl)amino]-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one trifluoroacetate,

25 To a solution of the product from example 12 step f) (100 mg) in dry THF (5 ml) was added [[[(1,1-dimethylethyl)dimethylsilyl]oxy]-acetaldehyde (49 mg) followed by sodium triacetoxyborohydride (61 mg) and the mixture stirred for 1 hour. The mixture was acidified with concentrated hydrochloric acid, stirred at room temp for 1 hour then  
30 evaporated to dryness. The product was purified (HPLC, Novapak<sup>®</sup> C18 column, 0.1% aqueous TFA:acetonitrile, gradient elution 75:25 to 5:95 over 15 minutes) to afford the title compound (0.021g).

MS (APCI) 428 ( $M+H^+$ , 100%).

35 NMR  $\delta$ H ( $d_6$ -DMSO) 7.39-7.29 (2H, m), 7.17-7.12 (1H, m), 6.92 (1H, m), 4.91 (1H, s), 4.48-4.32 (3H, m), 3.54 (2H, m), 2.94-2.82 (4H, m), 1.12 (3H, m).



**EXAMPLE 14**

**5-[[[(2,3-difluorophenyl)methyl]thio]-7-[[[(1*R*)-2-(dimethylamino)-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,**

Prepared by the method of example 13 using the product of example 12, step f) and 40 % aqueous formaldehyde solution.

MS (APCI) 412 (M+H<sup>+</sup>, 100%).

NMR  $\delta$ H (*d*<sub>6</sub>-DMSO) 12.00 (1H, s), 7.39-7.31 (2H, m), 7.18-7.09 (2H, m), 4.39 (2H, q), 4.30 (1H, m), 3.31 (6H, bs), 2.43-2.38 (1H, m), 2.24-2.0 (1H, m), 1.07 (3H, d).

**EXAMPLE 15**

**5-[[[4-(2-aminoethoxy)-3-chlorophenyl]methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one trifluoroacetate,**

**(a) 2-(2-chloro-4-formylphenoxy)acetamide,**

To a solution of 3-chloro-4-hydroxybenzaldehyde (10g) in methanol (100 ml) was added 1.0 M potassium t-butoxide (64 ml). To the mixture was added 2-chloroacetamide (5.96 g) and the mixture heated under reflux overnight. The mixture was evaporated to the residue triturated with water (500 ml) and the solid collected to give the subtitle compound (4.4g).

NMR  $\delta$ H (CDCl<sub>3</sub>) 9.89 (1H, s), 7.97 (1H, d), 7.82 (1H, dd), 7.04 (1H, d), 6.73 (1H, s), 5.87 (1H, s), 4.63 (2H, s).

**(b) 2-[2-chloro-4-(hydroxymethyl)phenoxy]acetamide,**

To a solution of the product from example 15 step a) (4.4g) in ethanol (500 ml) was added sodium borohydride (1.56 g) and the mixture allowed to stir for 1 hour. Acidified with glacial acetic acid, evaporated to dryness and extracted into ethyl acetate, washed with water to give the subtitle compound (4.3g).

NMR  $\delta$ H (CDCl<sub>3</sub>) 7.44 (1H, d), 7.29 (1H, d), 6.90 (1H, d), 6.81 (1H, s), 5.85 (1H, s), 4.63 (2H, s), 4.48 (2H, s), 1.96 (1H, s).

**(c) 2-[4-[(acetylthio)methyl]-2-chlorophenoxy]acetamide,**

Diisopropylazocarboxylate (5.5 ml) was added to a stirred solution of triphenylphosphine (7.31 g) in THF at 0°C. Upon completion of addition a colourless precipitate deposited. To this suspension was added a mixture of the product from example 15 step b) (3.0 g) and thiolacetic acid (2.00 ml) in THF (30 ml) at 0°C. The mixture was allowed to attain room temp overnight, evaporated to dryness and the residue purified (SiO<sub>2</sub>, 10% ethyl acetate: 90% ether as eluant) to give the subtitle compound (3.5g).

NMR δH (CDCl<sub>3</sub>) 7.35 (1H, d), 7.17 (1H, dd), 6.84 (1H, d), 6.76 (1H, s), 5.81 (1H, s), 4.54 (2H, s), 4.04 (2H, s), 2.35 (3H, s).

**(d) 2-[2-chloro-4-(mercaptomethyl)phenoxy]acetamide,**

To a solution of the product from example 15 step c)(1.0g) in methanol (50 ml) was added sodium hydroxide pellets (0.15 g) and the mixture stirred for 2 days. The mixture was diluted with water and the subtitle compound collected by filtration. (0.7 g).

NMR δH (*d6* DMSO) 7.44 (1H, s), 7.38 (1H, d), 7.21 (1H, dd), 6.98(1H, d), 4.55 (2H, s), 3.76 (2H, s).

**(e) 7-[[[(1R)-2-hydroxy-1-methylethyl]amino]-5-[(phenylmethyl)sulfonyl]thiazolo[4,5-*d*]pyrimidin-2(3H)-one,**

To a solution of the product from example 3 step d)(240 mg) in acetonitrile (100 ml) and water (100 ml) was added oxone (2.4 g) and the mixture heated at 40 deg for 2 hours. The acetonitrile was removed by rotary evaporation and the subtitle compound collected by filtration (235 mg)

MS (APCI) 381 (M+H<sup>+</sup>, 100%).

**(f) 5-[[[4-(2-aminoethoxy)-3-chlorophenyl]methyl]thio]-7-[[[(1R)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3H)-one trifluoroacetate,**

To a mixture of the product from example 15 step e) (100 mg), the product from example 15 step d) (329 mg) and sodium borohydride (50 mg) in a solution of DMSO (1 ml) and

ethanol (10 ml) was heated at 55-60°C for 12 hours. The reaction mixture was evaporated to dryness and the residue purified (HPLC, Novapak® C18 column, 0.1% aqueous TFA:acetonitrile, gradient elution 95:5 to 5:95 over 15 minutes) to afford the title compound (0.023g).

MS (APCI) 442 (M+H<sup>+</sup>, 100%).

NMR  $\delta$ H (*D*<sub>2</sub>O) 7.46 (1H, bs), 7.32 (1H, d), 7.00 (1H, d), 4.36-4.20 (5H, m), 3.61 (2H, m), 3.46 (2H, m), 1.20 (3H, d).

#### EXAMPLE 16

**5-[[3-Chloro-4-methoxyphenyl)methyl]thio]-7-[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

##### a) 3-chloro-4-methoxybenzenemethanethiol

Thiourea (3.04g, 0.04 mol) was added to a solution of 3-chloro-4-methoxybenzyl bromide (4.0g, 0.02 mol) in ethanol (200 ml) and refluxed for 16 hours. The reaction mixture was concentrated *in vacuo* and the residue was subsequently dissolved in aqueous sodium hydroxide solution (30g, 0.75 mol in 300 ml water) and heated at 80°C for one hour. The reaction mixture was cooled with an ice bath and acidified by addition of concentrated hydrochloric acid. The product was isolated by extraction three times into diethyl ether. The combined organic phases were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*, to give the sub-title compound as a colourless oil in 83% yield (3.0g).

NMR  $\delta$ H (CDCl<sub>3</sub>) 7.34 (1H, m), 7.18 (1H, dd), 6.86 (1H, d), 3.89 (3H, s), 3.68 (2H, d), 1.76 (1H, t).

##### b) 5-[[3-Chloro-4-methoxyphenyl)methyl]thio]-7-[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

3-chloro-4-methoxybenzenemethanethiol (0.128g, 0.68 mmol), prepared in example 16 step a), the product of example 15 step e) (0.130g, 0.349 mmol), and sodium borohydride (0.026g, 0.68 mmol) were refluxed at 50°C in a mixture of dimethylsulfoxide (6 ml) and ethanol (10 ml). After 3 hours and again after five hours reaction time, further portions of

sodium borohydride (0.05g, 1.3 mmol) in ethanol (2 ml) were added to the reaction and reflux at 50°C was continued until conversion was complete by hplc ms (15 hours in total). The reaction mixture was neutralised by addition of concentrated hydrochloric acid and the ethanol removed *in vacuo*. The residue was purified by reverse phase chromatography on Symmetry C8, eluting with a gradient of 25% to 95% acetonitrile in 0.1M aqueous ammonium acetate over 10 minutes. The product was freeze dried from methanol/water/acetonitrile to obtain the sub-title compound in 33% yield as a white lyophylate (0.046g).

MS (APCI) 413 (M+H<sup>+</sup>, 100%).

NMR  $\delta$ H (*d*<sub>6</sub>-DMSO) 12.39 (1H, bs), 7.47 (1H, m), 7.36 (1H, m), 7.25 (1H, d), 7.06 (1H, d), 4.72 (1H, t), 4.32-4.21 (3H, m), 3.82 (3H, s), 3.49-3.30 (2H, m), 1.11 (3H, d).

#### EXAMPLE 17

**5-[[3-Chloro-2-fluorophenyl)methyl]thio]-7-[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

##### **a) 3-chloro-2-fluorobenzenemethanethiol**

The sub-title compound was prepared as a colourless oil in 65% yield (2.51g) by the method described in example 16 step a) from 3-chloro-2-fluorobenzyl bromide (5.0g, 0.022 mol).

NMR  $\delta$ H (CDCl<sub>3</sub>) 7.32-7.21 (2H, m), 7.04 (1H, t), 3.75 (2H, d), 1.90 (1H, t).

##### **b) 5-[[3-Chloro-2-fluorophenyl)methyl]thio]-7-[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

The title compound was prepared by the method described in example 16 step b) from 3-chloro-2-fluorobenzenemethanethiol, prepared in example 17 step a), and the product of example 15 step e).

The product was obtained in 12% yield as a white lyophylate (0.038g).

M.P 234-5 °C

MS (APCI) 401 (M+H<sup>+</sup>, 100%).

NMR  $\delta$ H (*d*<sub>6</sub>-DMSO) 12.4 (1H, bs), 7.55 (1H, m), 7.48 (1H, t), 7.26 (1H, d), 7.17 (1H, t), 4.72 (1H, bs), 4.38 (2H, m), 4.19 (1H, m), 3.3 (2H, m), 1.08 (3H, d).

#### EXAMPLE 18

5 5-[[[(2,3-Difluorophenyl)methyl]thio]-7-[(3*R*,4*R*)-4-hydroxypyrrolidin-3-yl]amino]-thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

10 (a) 3-[[[2-amino-5-[[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-4-hydroxy-(3*R*,4*R*)-1-pyrrolidinecarboxylic acid, 1,1-dimethylethyl ester

(3*R*,4*R*)- 3-Amino-4-hydroxy-1-pyrrolidinecarboxylic acid, 1,1-dimethylethyl ester (0.73g), diisopropylethylamine (1.0 ml) and the product of example 4 step b), were stirred 15 in NMP (10ml) at 100°C for 28hrs. The cooled mixture was poured onto water and the solid produced collected, washed with water and air dried. The crude material was purified (SiO<sub>2</sub>, ethyl acetate as eluant) to give the subtitle compound as a colourless solid (0.58g). m.p. 182-5°C

MS (APCI) 511 (M+H, 100%).

20 (b) 3-[[[2-Bromo-5-[[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-4-hydroxy-(3*R*,4*R*)-1-pyrrolidinecarboxylic acid, 1,1-dimethylethyl ester

Prepared by the method of example 1 step e), using the product of example 18 step a).

25 MS (APCI) 572 (M-H<sup>+</sup>, 100%).

30 (c) 3-[[[5-[[[(2,3-Difluorophenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]-4-hydroxy-(3*R*,4*R*)-1-pyrrolidinecarboxylic acid, 1,1-dimethylethyl ester

Prepared by the method of example 1 step f), using the product of example 18 step b).

MS (APCI) 526 (M+H<sup>+</sup>, 100%).

(d) 5-[[[(2,3-Difluorophenyl)methyl]thio]-7-[(3*R*,4*R*)-4-hydroxypyrrolidin-3-yl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

Prepared by the method of example 1 step g), using the product of example 18 step c).

m.p. 270°C(dec)

MS (APCI) 412 (M+H<sup>+</sup>, 100%).

NMR δH (*d*<sub>6</sub>-DMSO) 7.32 (2H, m), 7.14 (1H, m), 6.46 (1H, d), 5.57 (1H, s), 4.39 (2H, s),  
5 4.30 (2H, m), 3.39 (2H, m), 3.12 (1H, dd), 2.98 (1H, d).

#### EXAMPLE 19

5-[[[(2,3-Difluorophenyl)methyl]thio]-7-[(3*R*)-pyrrolidin-3-ylamino]thiazolo[4,5-  
10 *d*]pyrimidin-2(3*H*)-one dihydrochloride

(a) 3-[[[2-Amino-5-[[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-  
yl]amino]-(3*R*)-1-pyrrolidinecarboxylic acid, 1,1-dimethylethyl ester

15 Prepared by the method of example 18 step a) using (*R*)-3-amino-1-pyrrolidinecarboxylic acid, 1,1-dimethylethyl ester and the product of example 4 step b).

MS (APCI) 495 (M+H<sup>+</sup>, 100%).

20 (b) 3-[[[2-Bromo-5-[[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(3*R*)-1-pyrrolidinecarboxylic acid, 1,1-dimethylethyl ester

Prepared by the method of example 1 step e), using the product of example 19 step a).

25 MS (APCI) 559 (M+H<sup>+</sup>, 100%).

(c) 3-[[[5-[[[(2,3-Difluorophenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-  
yl]amino]-(3*R*)-1-pyrrolidinecarboxylic acid, 1,1-dimethylethyl ester

30 Prepared by the method of example 1 step f), using the product of example 19 step b).

MS (APCI) 510 (M+H<sup>+</sup>, 100%).

(d) 5-[[[(2,3-Difluorophenyl)methyl]thio]-7-[(3*R*)-pyrrolidin-3-ylamino]thiazolo[4,5-  
*d*]pyrimidin-2(3*H*)-one, dihydrochloride

Prepared by the method of example 1 step g), using the product of example 19 step c) then converted to the salt.

m.p. 178-181°C

MS (APCI) 396 (M+H<sup>+</sup>, 100%).

5 NMR  $\delta$ H (*d*<sub>6</sub>-DMSO) 12.75 (1H,s), 9.19 (2H,bd), 7.91 (1H, d), 7.37 (2H,m), 7.17 (1H, m), 4.66 (1H, m), 4.43 (2H, dd), 3.10-3.50 (4H, m), 2.17 (1H, m), 1.96 (1H, m).

#### EXAMPLE 20

10 7-[[*(1R)*-2-Hydroxy-1-methylethyl]amino]-5-[[*(2-methyl-4-thiazolyl)*methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

##### (a) 6-Amino-2-[[*(2-methyl-4-thiazolyl)*methyl]thio]- 4(3*H*)-pyrimidinone

15 4- Amino-6-hydroxy-2-mercaptopyrimidine hydrate (16.1g) and powdered sodium hydroxide (8.0g) was stirred in dry DMF (100ml) for 20 mins. 4-Chloromethyl-2-methylthiazole hydrochloride monohydrate (20g) was added portionwise and the resulting suspension stirred 18hrs. The mixture was poured onto water and the solid collected, washed with water and dried to afford the sub-title compound (24.3g)

20 MS (APCI) 255 (M+H<sup>+</sup>, 100%).

##### (b) 2-Amino-5-[[*(2-methyl-4-thiazolyl)*methyl]thio]thiazolo[4,5-*d*]pyrimidin-7(6*H*)-one

25 The product from example 20 step a) (24.3g) and potassium thiocyanate (37.1g) was stirred in dry DMF (400ml) with pyridine (13.1ml) at 0°C. Bromine (4.5ml) was added over 1hr. After stirring 2hrs the mixture was poured into water. The resulting solution was concentrated to low volume then water added. The resulting solid was collected, taken up in 2M hydrochloric acid and precipitated by the addition of saturated sodium bicarbonate solution. The solid was collected, washed with water and dried to give the sub-title compound, (8.7g).

30 MS (APCI) 312 (M+H<sup>+</sup>, 100%).

##### (c) 7-Chloro-5-[[*(2-methyl-4-thiazolyl)*methyl]thio]thiazolo[4,5-*d*]pyrimidin-2-amine

Prepared by the method of example 1 step c), using the product of example 20 step b), (4.3g).

MS (APCI) 330/332 (M+H<sup>+</sup>), 330 (100%).

**(d) (2R)-2-[[2-Amino-5-[[2-methyl-4-thiazolyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1-propanol**

Prepared by the method of example 18 step a), using the product of example 20 step c),

m.p. 220-2°C

MS (APCI) 369 (M+H, 100%).

**(e) (2R)-2-[[2-Bromo-5-[[2-methyl-4-thiazolyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1-propanol**

Prepared by the method of example 1 step e), using the product of example 20 step d).

MS (APCI) 433 (M+H<sup>+</sup>, 100%).

**(f) (2R)-2-[[2-Methoxy-5-[[2-methyl-4-thiazolyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1-propanol**

Prepared by the method of example 1 step f), using the product of example 20 step e).

MS (APCI) 384 (M+H<sup>+</sup>, 100%).

**(g) 7-[[2-Hydroxy-1-methylethyl]amino]-5-[[2-methyl-4-thiazolyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

Prepared by the method of example 1 step g), using the product of example 20 step f).

m.p. 208-9°C

MS (APCI) 370 (M+H<sup>+</sup>, 100%).

NMR  $\delta$ H (*d*<sub>6</sub>-DMSO) 12.37 (1H,s), 7.35 (1H,s), 7.32 (1H, d), 4.73 (1H,t), 4.36 (2H, s), 4.21 (1H, m), 3.38 (2H, m), 2.62 (3H, s), 1.10 (3H, d).



**EXAMPLE 21**

**7-[[2-Hydroxy-1-(hydroxymethyl)ethyl]amino]-5-[[2-methyl-4-thiazolyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

**(a) 2-[[2-amino-5-[[2-methyl-4-thiazolyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]- 1,3-propanediol**

Prepared by the method of example 18 step a), using the product of example 20 step c) and  
2-amino-1,3-propanediol  
m.p. 158-160°C  
MS (APCI) 385 (M+H, 100%).

**(b) 2-[[2-Bromo-5-[[2-methyl-4-thiazolyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]- 1,3-propanediol**

Prepared by the method of example 1 step e), using the product of example 21 step a).

MS (APCI) 448 (M+H<sup>+</sup>, 100%).

**(c) 2-[[2-Methoxy-5-[[2-methyl-4-thiazolyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]- 1,3-propanediol**

Prepared by the method of example 1 step f), using the product of example 21 step b).

MS (APCI) 400 (M+H<sup>+</sup>, 100%).

**(d) 7-[[2-Hydroxy-1-(hydroxymethyl)ethyl]amino]-5-[[2-methyl-4-thiazolyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

Prepared by the method of example 1 step g), using the product of example 21 step c).

m.p. 239-243°C

MS (APCI) 386 (M+H<sup>+</sup>, 100%).

NMR  $\delta$ H (*d*<sub>6</sub>-DMSO) 12.37 (1H,s), 7.38 (1H,s), 7.24 (1H, d), 4.67 (2H,t), 4.36 (2H, s), 4.20 (1H, m), 3.50 (4H, m), 2.62 (3H, s).

**EXAMPLE 22**

**7-[(2-Hydroxy-1,1-dimethylethyl)amino]-5-[[2-methyl-4-thiazolyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

**(a) 2-[[2-Amino-5-[[2-methyl-4-thiazolyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-2-methyl-1-propanol**

Prepared by the method of example 18 step a), using the product of example 20 step c) and 2-amino-2-methylpropanol

m.p. 250-252°C

MS (APCI) 383 (M+H, 100%).

**(b) 2-[[2-Bromo-5-[[2-methyl-4-thiazolyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-2-methyl-1-propanol**

Prepared by the method of example 1 step e), using the product of example 22 step a).

MS (APCI) 446 (M+H<sup>+</sup>, 100%).

**(c) 2-[[2-Methoxy-5-[[2-methyl-4-thiazolyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-2-methyl-1-propanol**

Prepared by the method of example 1 step f), using the product of example 22 step b).

MS (APCI) 398 (M+H<sup>+</sup>, 100%).

**(d) 7-[(2-Hydroxy-1,1-dimethylethyl)amino]-5-[[2-methyl-4-thiazolyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

Prepared by the method of example 1 step g), using the product of example 22 step c).

m.p. 231-2°C

MS (APCI) 384 (M+H<sup>+</sup>, 100%).

NMR δH (*d*<sub>6</sub>-DMSO) 12.36 (1H, s), 7.37 (1H, s), 6.61 (1H, bs), 4.80 (1H, t), 4.37 (2H, s), 3.55 (2H, d), 2.62 (3H, s), 1.31 (6H, s).

**EXAMPLE 23**

7-[(2-Hydroxy-1,1-dimethylethyl)amino]-5-[[[(2-methylphenyl)methyl]thio]  
thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one.

(a) 7-[(2-Hydroxy-1,1-dimethylethyl)amino]-5-[(phenylmethyl)sulphonyl]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one.

A stirred solution of the product from example 1 step g) (0.14g) in glacial acetic acid (30ml) was treated with peracetic acid (36/40 % in acetic acid, 2ml), stirred for 2h, then at 50°C for 1h. The solution was quenched with an excess of dimethyl sulphide and evaporated to give a gum.

MS (APCI) 395 (M+H<sup>+</sup>, 100%).

(b) 7-[(2-Hydroxy-1,1-dimethylethyl)amino]-5-[[[(2-methylphenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one.

The product from example 23 step (a) was taken up in DMSO (1.73ml), treated with potassium *t*-butoxide and divided into 3 portions. One portion was treated with 2-methylphenylmethyl mercaptan (0.053g), stirred at 50°C for 1h for 2h, neutralised with glacial acetic acid and subjected to preparative reverse phase HPLC on a 19 x 50mm symmetry C8 column using 10 to 60% acetonitrile in 0.1 % aqueous ammonium acetate over 6 min at 20 ml/min to give the titled compound.

MS (APCI) 377 (M+H<sup>+</sup>, 100%).

NMR δH (*d*<sub>6</sub>-DMSO) 1.33 (s, 6H); 2.35 (s, 3H); 3.57 (d, 2H); 4.33 (s, 2H); 4.82 (t, 1H); 6.57 (broad s, 1H); 7.12-7.20 (mult., 3H); 7.41 (d, 1H); 12.37 (broad s, 1H)

**EXAMPLE 24**

5-[(2-Furanylmethyl)thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

**(a) 7-[[[(1*R*)-2-Hydroxy-1-methylethyl]amino]-5-[(phenylmethyl)sulphonyl]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one.**

The subtitled compound was prepared from the product of example 3 step d), using the method of example 23, step (a)

MS (ES) 381 ( $M+H^+$ , 100%).

**(b) 5-[(2-Furanylmethyl)thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

The titled compound was prepared from the product of example 24 step (a), using the method of example 23, step (b) using furfuryl mercaptan

MS (APCI) 339 ( $M+H^+$ , 100%).

NMR  $\delta$ H (*d*<sub>4</sub>-methanol) 1.12 (d, 3H); 3.41-3.45 (mult., 1H); 3.49-3.53 (mult., 1H); 4.24-4.32 (mult., 3H); 6.18-6.22 (mult., 2H); 7.29 (broad s, 1H).

**EXAMPLE 25**

**7-[[[(1*R*)-2-Amino-1-methylethyl]amino]-5-[[[(3-chloro-2-fluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

**(a) [(1*R*)-2-amino-1-methyl-2-oxoethyl]carbamic acid, 9*H*-fluoren-9-ylmethyl ester**

A solution of D-Alaninamide hydrochloride (3g) in 10% sodium carbonate solution (50 ml) and dioxan (50 ml) was treated with Fmoc chloride (6.24g) in dioxane (40 ml) and allowed to stir overnight. The mixture was diluted with water (500 ml) and the product collected by filtration and dried *in vacuo* to give 9.0g of the subtitle compound.

MS (ESI) BP 311 (+H)

**(b) [(1*R*)-2-amino-1-methylethyl]carbamic acid, 9*H*-fluoren-9-ylmethyl ester**

To a solution of the product from example 25 step a) (6.9g) in THF (100 ml) was added borane-methylsulfide complex (4.4 ml) and the mixture heated under reflux for 2 hours.

The mixture was carefully quenched by the addition of methanol (100 ml), evaporated to dryness and the residue taken up into methanol (100 ml) and acidified to pH 1-2 with concentrated hydrochloric acid. Heated under reflux for 30 mins then evaporated to dryness. The residue was triturated with ether to give a solid, which was collected by filtration, dissolved in water and the free base precipitated by the addition of aqueous sodium bicarbonate solution to give the subtitle compound (3.1g).

MS (ESI) BP 297 (+H)

**(c) (2R)-[2-(9H-Fluoren-9-ylmethoxycarbonylamino)-propyl]carbamic acid, 1,1-dimethylethylester.**

To a stirred solution of the product from example 25 step b) (3.0g) in THF (100 ml) was added di-tert-butyl dicarbonate (2.2g) and the mixture stirred at room temp for 30 mins. The mixture was evaporated to dryness and the crude product purified (SiO<sub>2</sub>, dichloromethane as eluant) to give the subtitle compound (3.8 g).

NMR  $\delta$ H (CDCl<sub>3</sub>) 7.76 (2H, m), 7.42 (2H, m), 7.39-7.26 (4H, s), 5.01 (1H, s), 4.85 (1H, s), 4.38 (2H, d), 4.19 (1H, t), 3.77 (1H, m), 3.18 (2H, m), 1.27 (9H, s).

**(d) [(2R)-2-aminopropyl]carbamic acid, 1,1-dimethylethyl ester**

To a solution of the product from example 25 step c) (3.8g) in THF (100 ml) was added piperidine (5 ml) and the mixture allowed to stand for 1 hour at room temp. The mixture was evaporated to dryness and the residue purified (SiO<sub>2</sub>, 5% methanol:dichloromethane as eluant) to give the subtitle compound as a colourless oil (1.7g).

NMR  $\delta$ H (CDCl<sub>3</sub>) 4.95 (1H, s), 3.13 (1H, m), 2.99 (1H, m), 2.87 (1H, m), 1.38 (9H, s), 1.08 (3H, d).

**(e) [(2R)-2-[[2-amino-5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-7-yl]amino]propyl]carbamic acid, 1,1-dimethylethyl ester**

The product from example 1 step c) (2.0g) and the product from example 25 step d) (1.3g) in a solvent of NMP (10ml) containing Hunigs base (3 ml) was heated at 110 °C for 10 hours. The mixture was evaporated to dryness and purified (SiO<sub>2</sub>, (1:1) dichloromethane:ethyl acetate as eluant) to give the subtitle compound (1.9g).

MS (ESI) BP 447 (+H)

**(f) [(2*R*)-2-[[2-amino-5-[(phenylmethyl)sulfonyl]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]propyl]carbamic acid, 1,1-dimethylethyl ester**

To a solution of OXONE (7.0g) in water (400 ml) was added sodium hydrogen carbonate until the pH was adjusted to 7.4. To this solution was added a solution of the product from example 25 step e) (1.9g) in acetonitrile (100 ml) and the mixture heated at 40 °C for 2 hours. Upon completion of the reaction the acetonitrile was removed by rotary evaporation to give the subtitle compound (1.7g).

MS (ESI) BP 479 (+H)

**(g) 3-chloro-2-fluoro-benzenemethanethiol,**

A mixture of 3-chloro-2-fluorobenzylbromide (5.0g), thiourea (3.4 g) in a solvent of ethanol (200 ml) was heated under reflux for 16 hours. The mixture was evaporated to dryness and to the residue was added a solution of sodium hydroxide (30 g) in water (300 ml) and the mixture heated under reflux for 1 hour. Allowed to cool to room temperature and acidified with concentrated hydrochloric acid, the product was extracted into ether to give the subtitle compound as an oil (2.51 g).

NMR  $\delta$ H (CDCl<sub>3</sub>) 7.32-21 (2H, m), 7.04 (1H, t), 3.75 (2H, d), 1.90 (1H, t).

**(h) [(2*R*)-2-[[2-amino-5-[[3-chloro-2-fluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]propyl]carbamic acid, 1,1-dimethylethyl ester**

To a mixture of the product from example 25 step f) (1.2g), the product from example 25 step g) (1.6 g) in a mixed solvent of ethanol (30 ml) and DMSO (5 ml) was added sodium borohydride (100 mg) and the mixture heated at 50°C for 2 hours. The ethanol was removed by rotary evaporation and the crude product extracted into ethyl acetate and washed with water. The subtitle compound was obtained by purification (SiO<sub>2</sub>, 1:1)dichloromethane :ethyl acetate as eluant) to give (1.95g).

MS (ESI) BP 499 (+H)

(i) [(2*R*)-2-[[2-bromo-5-[[[(3-chloro-2-fluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]propyl]carbamic acid, 1,1-dimethylethyl ester

Prepared by the method of example 1 step e), using the product of example 25 step h).

MS (APCI) 562 (M+H<sup>+</sup>, 100%).

(j) [(2*R*)-2-[[5-[[[(3-chloro-2-fluorophenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]propyl]carbamic acid, 1,1-dimethylethyl ester

Prepared by the method of example 1 step f), using the product of example 25 step i).

MS (APCI) 514 (M+H<sup>+</sup>, 100%).

(k) 7-[[[(1*R*)-2-Amino-1-methylethyl]amino]-5-[[[(3-chloro-2-fluorophenyl)methyl]thio]-thiazolo[4,5-*d*]pyrimidin-2-(3*H*)-one

Prepared by the method of example 1 step g), using the product of example 25 step j).

M.P 241-3 °C

MS (APCI) 400 (M+H<sup>+</sup>, 100%).

NMR δH (*d*<sub>6</sub>-DMSO) 7.56 (1H, m), 7.49 (1H, m), 7.17 (1H, m), 7.05 (1H, bs), 4.44 (1H, m), 4.39 (2H, ab), 2.92 (2H, d), 1.13 (3H, d).

## EXAMPLE 26

(2*S*)-2-[[5-[[[(2,3-Difluorophenyl)methyl]thio]-2,3-dihydro-2-oxothiazolo[4,5-*d*]pyrimidin-7-yl]amino]-3-hydroxy-propanamide

(a) (2*S*)-2-[[2-amino-5-[[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-3-hydroxy-propanamide

The subtitled compound was prepared according to example 2 step (a) using the product of example 4 step b) (2g, 6 mmol), l-serinamide (0.66g, 6 mmol), NMP (80 ml), and diisopropylethylamine (2 ml) to give the subtitled compound (1.36g)

Mp 145-151°C

MS (APCI) 413 (M+H<sup>+</sup>, 100%).

NMR  $\delta$ H (*d*<sub>6</sub>-DMSO) 8.10 (2H, brs), 7.40-7.07 (6H, m), 4.57 (1H, q), 4.43 (1H, d), 4.36 (1H, d), 3.71 (2H, d).

5

**(b) (2*S*)-2-[[5-[[[(2,3-Difluorophenyl)methyl]thio]-2,3-dihydro-2-oxothiazolo[4,5-*d*]pyrimidin-7-yl]amino]-3-hydroxy-propanamide**

Prepared by consecutive use of the methods of example 1 steps e), f), and g), using the product of example 26 step (a). The compounds formed during the separate steps were not purified or characterised.

10

MS (APCI) 414 (M+H<sup>+</sup>, 100%).

NMR  $\delta$ H (*d*<sub>6</sub>-DMSO) 12.47 (1H, br), 7.47 (1H, br), 7.42 (1H, s), 7.34 (2H, m), 7.13 (1H, m), 7.09 (1H, s), 4.90 (1H, t), 4.58 (1H, m), 4.39 (2H, m), 3.70 (2H, m).

15

#### EXAMPLE 27

**7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]-5-[(2-thienylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

20

**a) 7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]-5-[(2-thienylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

The title compound was prepared by the method described in example 16 step b) from the product of example 15 step e) (0.300g, 0.79mmol) and 2-thiophenemethanethiol (0.32ml, 3.9mmol).

25

The product was obtained in low 3% yield as a white lyophylate (0.010g).

MS (APCI) 355 (M+H<sup>+</sup>, 100%).

30

NMR  $\delta$ <sub>H</sub> (*d*<sub>6</sub>-DMSO) 12.50 (1H, bs), 7.36 (1H, m), 7.16 (1H, bs), 7.07 (1H, m), 6.92 (1H, m), 4.72 (1H, bs), 4.55 (2H, d), 4.26 (1H, m), 3.44 (2H, m), 1.12 (3H, d).



**EXAMPLE 28**

7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]-5[[[3-methyl-4-(methylsulfonyl)phenyl]methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

**a) 3-methyl-4-(methylthio)benzaldehyde**

Tin (IV) chloride (13.6ml, 0.116mol) was added to an ice-bath cooled solution of 1-methyl-2-(methylthio)benzene (10g, 0.073mol) in anhydrous dichloromethane (200ml) under nitrogen and stirred for a further 2 hours at 0°C.  $\alpha,\alpha$ -Dichloromethyl methyl ether (6.56ml, 0.073mol) was introduced and the reaction stirred for 1 hour at <10°C before the cooling was removed. After attaining room temperature, the reaction mixture was poured into ice/water (400ml), stirred and then extracted with dichloromethane (x3). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, concentrated onto silica gel and purified by flash chromatography, eluting with diethyl ether / isohexane (10:1) to yield the sub-title compound as a brown oil (6.54g) in 54% yield.

GCMS 166 ( $M^+$ , 100%).

NMR  $\delta_H$  ( $CDCl_3$ ) 9.91 (1H, s), 7.68 (1H, m), 7.62 (1H, s), 7.24 (1H, t), 2.54 (3H, s), 2.36 (3H, s).

**b) 3-methyl-4-(methylthio)benzenemethanol**

Sodium borohydride (1.40g, 0.037mol) was added to an ice-bath cooled solution of the product of example 28 step a) (6.16g, 0.037mol) in ethanol (50ml). After 1 hour, the reaction mixture was neutralised by careful addition of aqueous hydrochloric acid (2 molar) and concentrated *in vacuo* to remove the organic solvent. The remaining aqueous solution was then extracted with ethyl acetate (x3). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to yield the sub-title compound as a brown oil (6g) in quantitative yield.

GCMS 168 ( $M^+$ , 100%).

NMR  $\delta_H$  ( $CDCl_3$ ) 7.18 (3H, m), 4.62 (2H, bs), 2.46 (3H, s), 2.33 (3H, s).

**c) 3-methyl-4-(methylsulfonyl)benzenemethanol**

3-chloroperoxybenzoic acid (57-86% grade, 20.4g) was stirred in dichloromethane (150ml), dried over anhydrous magnesium sulfate and then filtered. The filtrate was added dropwise over 1 hour to an ice-bath cooled, stirred solution of the product from example 28 step b) (5.67g, 0.034mol) in dichloromethane (50ml). The reaction mixture was filtered and the filtrate washed with aqueous sodium hydrogen carbonate solution followed by aqueous sodium dithionite solution (10g Na<sub>2</sub>O<sub>4</sub>S<sub>2</sub> in 150ml water). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* before purification by flash chromatography, eluting with dichloromethane / methanol (100:2). The sub-title compound was obtained as a yellow oil (5.52g) in 82% yield.

MS (APCI) 201.1 (M+H<sup>+</sup>, 94.3%).

NMR  $\delta_H$  (CDCl<sub>3</sub>) 7.87 (1H, d), 7.38 (2H, m), 5.40 (1H, q), 4.56 (2H, d), 3.18 (3H, s), 2.61 (3H, s).

**d) 3-methyl-4-(methylsulfonyl)benzenemethanethiol acetate**

Diethyl azodicarboxylate (4.33ml, 0.028mol) was added to an ice-bath cooled solution of triphenylphosphine (7.20g, 0.028mol) in tetrahydrofuran (40ml). To the resulting suspension was added a solution of the product from example 28 step c) (5.5g, 0.028mol) dissolved in tetrahydrofuran (20ml). After the precipitate had dissolved, thiolacetic acid was added to the reaction solution and the cooling was removed. After 16 hours at room temperature, the reaction was concentrated onto silica gel and purified by flash chromatography, eluting with isohexane / ethyl acetate (2:1). The sub-title compound was obtained as a pink solid (2.46g) in 35% yield.

NMR  $\delta_H$  (*d*<sub>6</sub>-DMSO) 7.84 (1H, d), 7.36 (2H, m), 4.16 (2H, s), 3.19 (3H, s), 2.61 (3H, s), 2.37 (3H, s).

**e) bis[[3-methyl-4-(methylsulfonyl)phenyl]methyl]disulfide**

A mixture of the product of example 28 step d) (1.98g, 7.66mmol) and 7 molar methanolic/ammonia (30ml) was stirred for 24 hours. The product precipitated out of solution as a white solid and was isolated by filtration and dried *in vacuo*. The filtrate was

similarly treated with 7 molar ammonia in methanol and yielded a second crop of solid, white product. In total, the sub-title compound was obtained in 32% yield (0.534g).

MS (APCI) 451 ( $M+NH_4^+$ , 98.9%).

5 NMR  $\delta_H$  ( $d_6$ -DMSO) 7.88 (2H, s), 7.38-7.34 (4H, m), 3.88 (4H, s), 3.20 (6H, s), 2.64 (6H, s).

**f) 7-[[[(1R)-2-hydroxy-1-methylethyl]amino]-5-[[[3-methyl-4-(methylsulfonyl)phenyl]methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3H)-one**

10

The title compound was prepared by the method described in example 16 step b) using the product from example 15 step e) (0.20g, 0.53mmol) and the product from example 28 step e) (0.34g, 0.79mmol) to yield 11% product as a white lyophylate (0.025g).

15 MS (APCI) 441 ( $M+H^+$ , 100%).

NMR  $\delta_H$  ( $d_6$ -DMSO) 12.40 (1H, s), 7.81 (1H, d), 7.52 (2H, m), 7.33 (1H, d), 4.74 (1H, t), 4.35 (2H, s), 4.19 (1H, m), 3.41 (1H, m), 3.34-3.28 (1H, m), 3.18 (3H, s), 2.61 (3H, s), 1.08 (3H, d).

20 **EXAMPLE 29**

**5-[[[3-chloro-4-(trifluoromethoxy)phenyl]methyl]thio]-7-[[[(1R)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3H)-one**

25 **a) 3-chloro-4-(trifluoromethoxy)benzenemethanethiol**

To a solution of 3-chloro-4-(trifluoromethoxy)benzylbromide (5g) in ethanol (100 ml) was added thiourea (5g) and the mixture heated under reflux for 2 hours. The mixture was evaporated to dryness and the residue taken up into water (100 ml). To this solution was  
30 added sodium hydroxide pellets (3 g) and the mixture heated under reflux for 1 hour. The mixture was allowed to cool to room temperature and acidified with concentrated hydrochloric acid, the mixture was extracted with ether, dried and evaporated to give the subtitle compound as a colourless waxy solid (3.5g).

35 NMR  $\delta_H$  ( $CDCl_3$ ) 7.35-7.09 (3H, m), 3.58 (2H, s).

**b) 5-[[[3-chloro-4-(trifluoromethoxy)phenyl]methyl]thio]-7-[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

The title compound was prepared by the method described in example 16 step b) using the product from example 15 step e) (0.40g, 1.05mmol) and the product from example 29 step a) (0.71g, 1.5mmol) to yield 10% product as a white lyophylate (0.046g).

MS (APCI) 467 (M+H<sup>+</sup>, 100%).

NMR  $\delta_{\text{H}}$  (*d*<sub>6</sub>-DMSO) 12.42 (1H, s), 7.75 (1H, m), 7.52 (2H, m), 7.43 (1H, d), 4.72 (1H, t), 4.34 (2H, d), 4.18 (1H, quintet), 3.46-3.27 (2H, m), 1.07 (3H, d).

**EXAMPLE 30**

**5-[[[2-fluoro-3-(trifluoromethyl)phenyl]methyl]thio]-7-[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

**a) 2-fluoro-3-(trifluoromethyl)benzenemethanethiol**

The subtitle compound was prepared from 2-fluoro-(3-trifluoromethyl)benzylbromide (10 g) using the method of example 29 step a)

NMR  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 7.68-7.18 (3H, m), 3.74 (2H, s), 1.98 (1H, s).

**b) 5-[[[2-fluoro-3-(trifluoromethyl)phenyl]methyl]thio]-7-[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

The title compound was prepared by the method described in example 16 step b) using the product of example 15 step e) (0.47g, 1.23mmol) and the product of example 30 step a) (0.775g, 3.7mmol) to yield 5% product as a white lyophylate (0.025g).

MS (APCI) 435 (M+H<sup>+</sup>, 100%).

NMR  $\delta_{\text{H}}$  (*d*<sub>6</sub>-DMSO) 12.42 (1H, s), 7.92 (1H, t), 7.68 (1H, t), 7.35 (2H, m), 4.71 (1H, bs), 4.42 (2H, m), 4.16 (1H, quintet), 3.40-3.30 (2H, m), 1.07 (3H, d).

**EXAMPLE 31**

**5-[[[(2,3-difluorophenyl)methyl]thio]-7-[2-[(dimethylamino)ethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one monohydrochloride**

**(a) 2-Bromo-7-chloro-5-[[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidine**

The product of example 4 step (b) (8.0g) was suspended in bromoform (200ml) followed by addition of tert-butyl nitrite (8ml) and the whole heated at 60°C for 30 minutes. The solvents were removed by reduced pressure and the residue purified by column chromatography (silica – 1:1 dichloromethane/isohexane) to give a yellow solid (5.6g).

MS (APCI) 409/411 (M+H, 100%).

**(b) 7-chloro-5-[(2,3-difluorophenylmethyl)thio]-2-methoxythiazolo[4,5-*d*]pyrimidine**

The product of example 31 step a) (5.6g) was suspended in methanol (150ml) and potassium hydroxide powder (0.77g) added. The whole was stirred at room temperature for 2 hours. The mixture was adjusted to pH 7 with a few drops of concentrated hydrochloric acid before it was evaporated to dryness. Purified by column chromatography (silica – 3:2 to 1:1 isohexane/dichloromethane) to give white solid (2.0g).

MS (APCI) 360/362 (M+H, 100%).

**(c) 7-Chloro-5-[[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

The product from example 31 step (b) (2.0g) was dissolved in dioxan (150ml) followed by addition of concentrated hydrochloric acid (1ml) and water (1ml) and the whole heated at 40°C for 67 hours. The mixture was evaporated to dryness and purified by column chromatography (silica – dichloromethane) to give a white solid (1.4g).

MS (APCI) 346/348 (M+H, 100%).

**(d) 5-[[[(2,3-difluorophenyl)methyl]thio]-7-[2-[(dimethylamino)ethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one monohydrochloride**

The product from example 31 step (c) (1.4g) was dissolved in dry tetrahydrofuran (5ml) and to the solution was added N,N-dimethylethylenediamine (0.25g) in a finger bomb which was heated at 80°C for 24 hours. The solvents were removed by reduced pressure and the residue partitioned between ethyl acetate and brine. The combined organic extracts were dried (sodium sulfate) and evaporated by reduced pressure for the ensuing residue to be purified by column chromatography (silica – 5:1 ethyl acetate/methanol) to give the free base as a sticky solid (0.095g). This was converted to the monohydrochloride by suspending the solid in methanol (10ml) followed by addition of concentrated hydrochloric acid (3 drops) to ensure dissolution then water (100ml) for the compound to be freeze dried to give a brown powder (0.080g).

m.p. 263°C(dec.)

MS (APCI) 398 (M+H, 100%).

NMR  $\delta$ H ( $d_6$ -DMSO) 12.57 (1H,s), 10.22 (1H,s), 7.94(1H,t), 7.40(1H,m), 7.34(1H,m), 7.16(1H,m), 4.43(2H,s), 3.78(2H,s), 3.21(2H,m), 2.78(6H,d)

## EXAMPLE 32

**5-[[[(2-fluorophenyl)methyl]thio]-7-[[[(1R)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

**(a) 2-[[[2-amino-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol**

The product of example 1 step c) (25.0 g), *D*-Alaninol (12.3 g) and diisopropylethylamine (26.0 g) were diluted in *N*-methylpyrrolidinone (250 ml) and stirred at 100 °C for 24 h before cooling and pouring the reaction mixture into H<sub>2</sub>O (2.5 l). The precipitate was filtered and dried *in vacuo* before being preabsorbed onto silica gel. Chromatography using EtOAc, 4 % MeOH / EtOAc as eluents afforded the desired product as a yellow solid (9.0 g, 32 %).

MS (APCI) 347 (M+H, 100%).

**(b) 2-[(2-amino-5-mercaptothiazolo[4,5-*d*]pyrimidin-7-yl)amino]-(2*R*)-1-propanol**

Sodium metal was added portionwise to a solution of the product of example 32 step a) (5.0 g) in ammonia (150 ml) until a blue colouration persisted. Ammonium chloride was

then added and the solvent allowed to evaporate. The residue was dissolved in H<sub>2</sub>O (200 ml) and filtered before neutralising with 2M HCl solution. The grey precipitate was filtered, washed with H<sub>2</sub>O (200 ml) and dried *in vacuo* for 48 h to yield the subtitle compound as a brown solid (3.0 g).

MS (APCI) 258 (M+H, 100 %).

**(c) 2-[[2-amino-5-[[2-fluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol**

2-fluorobenzylbromide (0.369 g) was added portionwise to a solution of the product of example 32 step b) (0.5 g) and diisopropylethylamine (0.26 g) in DMSO / *N*-methylpyrrolidinone (4 ml / 0.5 ml) at 50 °C and stirring maintained for 1 h. The mixture was partitioned between H<sub>2</sub>O (200 ml) and EtOAc (120 ml). The organics were recovered and washed further with H<sub>2</sub>O (200 ml), dried over MgSO<sub>4</sub> and concentrated onto silica gel. The subtitle compound was purified by flash chromatography using DCM then EtOAc as eluents to yield a white solid (245 mg, 35 %).

MS (APCI) 366 (M+H, 100 %)

**(d) 2-[[2-bromo-5-[[2-fluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol**

Isoamyl nitrite (0.3 ml) was added to a suspension of the product of example 32 step c) (0.23 g) in bromoform (15 ml) and acetonitrile (15 ml) at 50 °C. Stirring was maintained for 10 min before concentrating to approximately 3 ml. The residue was purified by column chromatography using 20 % EtOAc / DCM as eluent to yield the subtitle compound as a yellow solid (102 mg, 38 %).

MS (APCI) 429 (M+H, 100 %).

**(e) 2-[[5-[[2-fluorophenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol**

Potassium hydroxide (27 mg) was added to a solution of the product of example 32 step d) (0.1 g) in MeOH (10 ml). The mixture was stirred for 24 h before neutralising to pH 7

with 2M HCl solution. The volatiles were removed *in vacuo* and the product used directly in the following step.

MS (APCI) 381 (M+H, 100 %).

5 **(f) 5-[[[(2-fluorophenyl)methyl]thio]-7-[[[(1R)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

10 The product of example 32 step e) was dissolved in 1,4-dioxane (50 ml), H<sub>2</sub>O (1 ml) and concentrated HCl solution (0.5 ml) and stirred for 20 h at 40 °C. The volatiles were removed under reduced pressure and the crude product purified by preparative HPLC to afford the subtitle compound as a white solid (21 mg).

MS (APCI) 367 (M+H, 100 %)

15 NMR  $\delta$ H (*d*<sub>6</sub>-DMSO) 12.40 (1H, s), 8.14-7.11 (5H, m), 4.72 (1H, t), 4.35 (2H, m), 4.22 (1H, m), 3.47-3.29 (2H, m), 1.10 (3H, d)

### EXAMPLE 33

20 **7-[[[(1R)-2-hydroxy-1-methylethyl]amino]-5-[[[(2-methoxyphenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

**(a) 2-[[[2-amino-5-[[[(2-methoxyphenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol**

25 Prepared by the method of example 32 step c), using the product of example 32 step b).

MS (APCI) 378 (M+H<sup>+</sup>, 100%).

30 **(b) 2-[[[2-bromo-5-[[[(2-methoxyphenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol**

Prepared by the method of example 32 step d), using the product of example 33 step a).

35 MS (APCI) 441 (M+H<sup>+</sup>, 100%).



**(c) 2-[[2-methoxy-5-[[2-methoxyphenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol**

Prepared by the method of example 32 step e), using the product of example 33 step b).

MS (APCI) 393 (M+H<sup>+</sup>, 100%).

**(d) 7-[[2-hydroxy-1-methylethyl]amino]-5-[[2-methoxyphenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

Prepared by the method of example 32 step f), using the product of example 33 step c).

MS (APCI) 379 (M+H<sup>+</sup>, 100%).

NMR  $\delta$ H (*d*<sub>6</sub>-DMSO) 7.40 (1H, dd), 7.22 (1H, dt), 6.97 (1H, d), 6.84 (1H, dt), 6.00 (1H, d), 4.25 (2H, m), 4.15 (1H, m), 3.83 (3H, s), 3.48-3.31 (2H, m), 1.10 (3H, d).

**EXAMPLE 34**

**7-[[2-hydroxy-1-methylethyl]amino]-5-[(2-phenoxyethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

**(a) 2-[[2-amino-5-[(2-phenoxyethyl)thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol**

Prepared by the method of example 32 step c), using the product of example 32 step b).

MS (APCI) 378 (M+H<sup>+</sup>, 100%).

**(b) 2-[[2-bromo-5-[(2-phenoxyethyl)thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol**

Prepared by the method of example 32 step d), using the product of example 34 step a).

MS (APCI) 441 (M+H<sup>+</sup>, 100%).

**(c) 2-[[2-methoxy-5-[(2-phenoxyethyl)thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol**

Prepared by the method of example 32 step e), using the product of example 34 step b).

MS (APCI) 393 (M+H<sup>+</sup>, 100%).

**(d) 7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]-5-[(2-phenoxyethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

Prepared by the method of example 32 step f), using the product of example 34 step c).

MS (APCI) 379 (M+H<sup>+</sup>, 100%).

NMR  $\delta$ H (*d*<sub>6</sub>-DMSO) 12.37 (1H, s), 7.30-7.26 (3H, m), 6.96-6.91 (3H, m), 4.71 (1H, t), 4.23-4.14 (3H, m), 3.46-3.28 (4H, m), 1.08 (3H, d)

**EXAMPLE 35**

**7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]-5-[[[(3-methylphenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

**(a) 2-[[2-amino-5-[[[(3-methylphenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol**

Prepared by the method of example 32 step c), using the product of example 32 step b).

MS (APCI) 362 (M+H<sup>+</sup>, 100%).

**(b) 2-[[2-bromo-5-[[[(3-methylphenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol**

Prepared by the method of example 32 step d), using the product of example 35 step a).

MS (APCI) 425 (M+H<sup>+</sup>, 100%).

(c) 2-[[2-methoxy-5-[[3-methylphenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol

Prepared by the method of example 32 step e), using the product of example 35 step b).

MS (APCI) 377 (M+H<sup>+</sup>, 100%).

(d) 7-[[1*R*]-2-hydroxy-1-methylethyl]amino]-5-[[3-methylphenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

Prepared by the method of example 32 step f), using the product of example 35 step c).

MS (APCI) 363 (M+H<sup>+</sup>, 100%).

NMR  $\delta$ H (*d*<sub>6</sub>-DMSO) 12.37 (1H, s), 7.23-7.16 (4H, m), 7.04 (1H, d), 4.73 (1H, t), 4.28 (2H, m), 4.24 (1H, m), 3.48-3.30 (2H, m), 2.28 (3H, s), 1.11 (3H, d).

#### EXAMPLE 36

5-[[2-fluoro-3-methylphenyl)methyl]thio]-7-[[1*R*]-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

(a) 2-[[2-amino-5-[[2-fluoro-3-methylphenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol

Prepared by the method of example 32 step c), using the product of example 32 step b).

MS (APCI) 380 (M+H<sup>+</sup>, 100%).

(b) 2-[[2-bromo-5-[[2-fluoro-3-methylphenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol

Prepared by the method of example 32 step d), using the product of example 36 step a).

MS (APCI) 443 (M+H<sup>+</sup>, 100%).

**(c) 2-[[5-[[[(2-fluoro-3-methylphenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol**

Prepared by the method of example 32 step e), using the product of example 36 step b).

MS (APCI) 395 (M+H<sup>+</sup>, 100%).

**(d) 5-[[[(2-fluoro-3-methylphenyl)methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

Prepared by the method of example 32 step f), using the product of example 36 step c).

MS (APCI) 381 (M+H<sup>+</sup>, 100%).

NMR δH (*d*<sub>6</sub>-DMSO) 12.39 (1H, s), 7.37-7.00 (4H, m), 4.72 (1H, t), 4.33 (2H, m), 4.22 (1H, m), 3.47-3.30 (2H, m), 2.23 (3H, s), 1.11 (3H, d)

**EXAMPLE 37**

**5-[[[(3-chlorophenyl)methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

**(a) 2-[[2-amino-5-[[[(3-chlorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol**

Prepared by the method of example 32 step c), using the product of example 32 step b).

MS (APCI) 382 (M+H<sup>+</sup>, 100%).

**(b) 2-[[2-bromo-5-[[[(3-chlorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol**

Prepared by the method of example 32 step d), using the product of example 37 step a).

MS (APCI) 445 (M+H<sup>+</sup>, 100%).

**(c) 2-[[5-[[[(3-chlorophenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol**

Prepared by the method of example 32 step e), using the product of example 37 step b).

MS (APCI) 397 (M+H<sup>+</sup>, 100%).

**(d) 5-[[[(3-chlorophenyl)methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

Prepared by the method of example 32 step f), using the product of example 37 step c).

MS (APCI) 383 (M+H<sup>+</sup>, 100%).

NMR  $\delta$ H (*d*<sub>6</sub>-DMSO) 12.40 (1H, s), 7.49 (1H, d), 7.43-7.30 (4H, m), 4.72 (1H, t), 4.32 (2H, m), 4.21 (1H, m), 3.48-3.26 (2H, m), 1.09 (3H, d).

**EXAMPLE 38**

**5-[[[(3-bromophenyl)methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

**(a) 2-[[2-amino-5-[[[(3-bromophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol**

Prepared by the method of example 32 step c), using the product of example 32 step b).

MS (APCI) 426 (M+H<sup>+</sup>, 100%).

**(b) 2-[[2-bromo-5-[[[(3-bromophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol**

Prepared by the method of example 32 step d), using the product of example 38 step a).

MS (APCI) 491 (M+H<sup>+</sup>, 100%).

**(c) 2-[[5-[[[(3-bromophenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol**

Prepared by the method of example 32 step e), using the product of example 38 step b).

MS (APCI) 443 (M+H<sup>+</sup>, 100%).

**(d) 5-[[[(3-bromophenyl)methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

Prepared by the method of example 32 step f), using the product of example 38 step c).

MS (APCI) 427 (M+H<sup>+</sup>, 100%).

NMR δH (*d*<sub>6</sub>-DMSO) 12.40 (1H, s), 7.63 (1H, t), 7.46-7.24 (4H, m), 4.72 (1H, t), 4.31 (2H, m), 4.21 (1H, m), 3.48-3.26 (2H, m), 1.10 (3H, d)

**EXAMPLE 39**

**5-[[[4-(difluoromethoxy)phenyl]methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

**(a) 2-[[2-amino-5-[[[4-(difluoromethoxy)phenyl]methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol**

Prepared by the method of example 32 step c), using the product of example 32 step b).

MS (APCI) 414 (M+H<sup>+</sup>, 100%).

**(b) 2-[[2-bromo-5-[[[4-(difluoromethoxy)phenyl]methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol**

Prepared by the method of example 32 step d), using the product of example 39 step a).

MS (APCI) 477 (M+H<sup>+</sup>, 100%).

**(c) 2-[[[5-[[[4-(difluoromethoxy)phenyl]methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol**

Prepared by the method of example 32 step e), using the product of example 39 step b).

MS (APCI) 429 (M+H<sup>+</sup>, 100%).

**(d) 5-[[[4-(difluoromethoxy)phenyl]methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

Prepared by the method of example 32 step f), using the product of example 39 step c).

MS (APCI) 415 (M+H<sup>+</sup>, 100%).

NMR  $\delta$ <sub>H</sub> (*d*<sub>6</sub>-DMSO) 12.38 (1H, s), 7.48 (2H, dt), 7.26 (1H, d), 7.19 (1H, t), 7.11 (2H, dd), 4.73 (1H, t), 4.31 (2H, m), 4.21 (1H, m), 3.47-3.30 (2H, m), 1.10 (3H, d)

**EXAMPLE 40**

**(+/-)-5-[[[2,3-difluorophenyl]methyl]thio]-7-[[2-hydroxy-1-(methoxymethyl)ethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

**(a) (+/-)-2-amino-3-methoxy-1-propanol hydrochloride**

To a suspension of DL- 3-methoxy-alanine (1.0g) in dry THF (100 ml) was added borane methylsulfide complex (10 ml) and the mixture heated under reflux for 16 hours. The mixture was then quenched with methanol while at reflux, evaporated to dryness and the residue taken up into methanolic hydrogen chloride (100 ml) and heated under reflux for a further 2 hours, evaporated to dryness to give the subtitle compound as a colourless gum (1.0g).

NMR  $\delta$ <sub>H</sub> (D<sub>2</sub>O) 3.40 (3H, s), 3.53-3.74 (4H, m), 3.81 (1H, m)

**(b) (+/-)-2-[[[2-amino-5-[[[2,3-difluorophenyl]methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-3-methoxy-1-propanol,**

Prepared by the method of example 12 step a) using the product of example 4 step b) and the product of example 40 step a).

MS (APCI) 414 (M+H<sup>+</sup>, 100%).

(c) (+/-)-2-[[2-chloro-5-[[2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-3-methoxy-1-propanol,

To a solution of the product from example 40 step b) (1.0g) in a mixture of concentrated hydrochloric acid (40 ml) and water (32 ml) cooled in ice water was added a solution of sodium nitrite (0.4 g) in water (5 mL), stirred at this temp for 2 hours. The mixture was then extracted into ethyl acetate, dried and evaporated to give the subtitle compound (0.6g).

MS (APCI) 434 (M+H<sup>+</sup>, 100%).

(d) (+/-)-2-[[5-[[2,3-difluorophenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]-3-methoxy-1-propanol,

Prepared by the method of example 1 step f), using the product of example 40 step c).

MS (APCI) 429 (M+H<sup>+</sup>, 100%).

(e) (+/-)-5-[[2,3-difluorophenyl)methyl]thio]-7-[[2-hydroxy-1-(methoxymethyl)ethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

Prepared by the method of example 1 step g), using the product of example 40 step d).

MS (APCI) 415 (M+H<sup>+</sup>, 100%).

#### EXAMPLE 41

7-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

(a) 2-[[2-amino-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1,3-propanediol,



Prepared by the method of example 12 step a) using the product of example 1 step c) and 2-amino-1,3-propanediol.

MS (APCI) 364 (M+H<sup>+</sup>, 100%).

NMR  $\delta$ H (*d*<sub>6</sub>-DMSO) 7.42-7.38 (1H, m), 7.28 (1H, t), 7.22 (1H, t), 5.30 (1H, d), 4.63 (1H, bs), 4.28 (2H, s), 4.03 (1H, m), 3.54-3.40 (4H, m).

**(b) 2-[[2-chloro-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1,3-propanediol,**

Prepared by the method of example 40 step c) and the product of example 41 step a)

MS (APCI) 384 (M+H<sup>+</sup>, 100%).

**(c) 2-[[2-methoxy-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1,3-propanediol,**

Prepared by the method of example 1 step f) and the product of example 41 step b)

MS (APCI) 379 (M+H<sup>+</sup>, 100%).

**(d) 7-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

Prepared by the method of example 1 step g) and the product of example 41 step c)

MS (APCI) 365 (M+H<sup>+</sup>, 100%).

#### EXAMPLE 42

**5-[[[(2-bromophenyl)methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

**(a) 2-[[2-amino-5-[[[(2-bromophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol**

Prepared by the method of example 32 step c), using the product of example 32 step b).

MS (APCI) 428 (M+H<sup>+</sup>, 100%).

**(b) 2-[[2-bromo-5-[[2-bromophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol**

Prepared by the method of example 1 step e), using the product of example 42 step a).

MS (APCI) 491 (M+H<sup>+</sup>, 100%).

**(c) 2-[[5-[[2-bromophenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol**

Prepared by the method of example 1 step f), using the product of example 42 step b).

MS (APCI) 443 (M+H<sup>+</sup>, 100%).

**(d) 5-[[2-bromophenyl)methyl]thio]-7-[[2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

Prepared by the method of example 1 step g), using the product of example 42 step c).

MS (APCI) 427 (M+H<sup>+</sup>, 100%).

NMR  $\delta$  H (*d*<sub>6</sub>-DMSO) 12.41 (1H, s), 7.65-7.14 (5H, m), 4.72 (1H, t), 4.42 (2H, s), 4.21 (1H, m), 3.47-3.30 (2H, m), 1.10 (3H, d)

**EXAMPLE 43**

**5-[[2,3-Difluorophenyl)methyl]thio]-7-[[2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one sodium salt**

The product from example 5 step d) was suspended in water and to this suspension was added 1 equivalent of 0.1 N sodium hydroxide solution, followed by the addition of a small aliquot of tetrahydrofuran to aid dissolution. The resultant solution was then lyophilised to give the title compound as a colourless solid.

MP 218-220 °C

MS (APCI) 385 (M+H<sup>+</sup>, 100%).

NMR  $\delta$ H ( $d_6$ -DMSO) 7.39-7.09 (3H, m), 5.60 (1H, d), 4.65 (1H, m), 4.34 (2H, q), 4.09 (1H, m), 3.44-3.27 (2H, m), 1.06(3H, d).

#### EXAMPLE 44

5-[[[3-Chloro-2-fluorophenyl)methyl]thio]-7-[[*(1R)*-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one sodium salt

Prepared as in example 43 using the product of example 17 step b)

MS (APCI) 401 ( $M+H^+$ , 100%).

#### EXAMPLE 45

(+/-)-5-[[[2,3-difluorophenyl)methyl]thio]-7-[[2-hydroxy-1-(methoxymethyl)ethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one sodium salt

Prepared by the method of example 43 using the product of example 40 step e).

MP >250°C

MS (APCI) 415 ( $M+H^+$ , 100%).

NMR  $\delta$ H ( $d_6$ -DMSO) 7.39-7.04 (3H, m), 5.51 (1H, d), 4.68 (1H, t), 4.34 (2H, q), 4.22 (1H, m), 3.51-3.35 (4H, m), 3.32(3H, s).

#### EXAMPLE 46

7-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one sodium salt

Prepared by the method of example 43 using the product from example 41 step d)

MP 231-2°C

MS (APCI) 365 ( $M+H^+$ , 100%).

NMR  $\delta$ H ( $d_6$ -DMSO) 7.41-7.18 (5H,m), 5.30 (1H,d), 4.63 (2H, s), 4.28 (2H,s), 4.06 (1H, m), 3.50 (4H, m).

**EXAMPLE 47**

7-[[*(1R)*-2-Hydroxy-1-methylethyl]amino]-5-[(phenylmethyl)thio]thiazolo[4,5-  
5 *d*]pyrimidin-2(3*H*)-one sodium salt

Prepared by the method of example 43 using the product of example 3 step d).

MP (shrinks 110) melts 221-225°C

10 MS (APCI) 349 (M+H<sup>+</sup>, 100%).

NMR δH (*d*<sub>6</sub>-DMSO) 7.41-7.18 (5H, m), 5.58 (1H, d), 4.65 (1H, t), 4.28 (2H, q), 4.11  
(1H, m), 3.49-3.31 (2H, m), 1.08 (3H, d).

**EXAMPLE 48**

15 5-[(5-chloro-1,2,3-thiadiazol-4-yl)thio]-7-[[*(1R)*-2-hydroxy-1-methylethyl]amino]-  
thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

(a) (2*R*)-2-[[2-amino-5-[(5-chloro-1,2,3-thiadiazol-4-yl)thio]thiazolo[4,5-*d*]pyrimidin-  
20 7-yl]amino]-1-propanol

Prepared by the method of example 32 step c), using the product of example 32 step b) and  
5-chloro-4-(chloromethyl)-1,2,3-thiadiazole.

25 MS (APCI) 390 (M+H<sup>+</sup>, 100%).

(b) (2*R*)-2-[[2-chloro-5-[(5-chloro-1,2,3-thiadiazol-4-yl)methyl]thio]thiazolo[4,5-  
*d*]pyrimidin-7-yl]amino]-1-propanol

30 Prepared by the method of example 40 step c) and using the product of example 48 step a)

MS (APCI) 409 (M+H<sup>+</sup>, 100%).

(c) (2*R*)-2-[[5-[(5-chloro-1,2,3-thiadiazol-4-yl)methyl]thio]-2-methoxythiazolo[4,5-  
35 *d*]pyrimidin-7-yl]amino]-1-propanol

Prepared by the method of example 1 step f) and using the product of example 48 step b)

MS (APCI) 405 (M+H<sup>+</sup>, 100%).

- 5 (d) 5-[(5-chloro-1,2,3-thiadiazol-4-yl)thio]-7-[[*(1R)*-2-hydroxy-1-methylethyl]amino]-thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

Prepared by the method of example 1 step g) and using the product of example 48 step c)

- 10 MS (APCI) 391(M+H<sup>+</sup>, 100%).

NMR  $\delta$ H (*d*<sub>6</sub>-DMSO) 12.39 (1H, s), 7.39 (1H, d), 4.76 (2H, AB), 4.70 (1H, t), 4.24 (1H, m), 3.48-3.30 (2H, m), 1.11 (3H, d)

15 **Pharmacological Data**

**Ligand Binding Assay**

- [<sup>125</sup>I]IL-8 (human, recombinant) was purchased from Amersham, U.K. with a specific activity of 2,000Ci/mmol. All other chemicals were of analytical grade. High levels of  
20 hrCXCR2 were expressed in HEK 293 cells (human embryo kidney 293 cells ECACC No. 85120602) (Lee *et al.* (1992) *J. Biol. Chem.* 267 pp16283-16291). hrCXCR2 cDNA was amplified and cloned from human neutrophil mRNA. The DNA was cloned into PCRScript (Stratagene) and clones were identified using DNA. The coding sequence was sub-cloned  
25 into the eukaryotic expression vector RccMV (Invitrogen). Plasmid DNA was prepared using Quiagen Megaprep 2500 and transfected into HEK 293 cells using Lipofectamine reagent (Gibco BRL). Cells of the highest expressing clone were harvested in phosphate-buffered saline containing 0.2%(w/v) ethylenediaminetetraacetic acid (EDTA) and centrifuged (200g, 5min.). The cell pellet was resuspended in ice cold homogenisation buffer [10mM HEPES (pH 7.4), 1mM dithiothreitol, 1mM EDTA and a panel of protease  
30 inhibitors (1mM phenyl methyl sulphonyl fluoride, 2 $\mu$ g/ml soybean trypsin inhibitor, 3mM benzamidine, 0.5 $\mu$ g/ml leupeptin and 100 $\mu$ g/ml bacitracin)] and the cells left to swell for 10 minutes. The cell preparation was disrupted using a hand held glass mortar/PTFE pestle homogeniser and cell membranes harvested by centrifugation (45 minutes, 100,000g, 4°C). The membrane preparation was stored at -70°C in homogenisation buffer supplemented  
35 with Tyrode's salt solution (137mM NaCl, 2.7mM KCl, 0.4mM NaH<sub>2</sub>PO<sub>4</sub>), 0.1%(w/v) gelatin and 10%(v/v) glycerol.

All assays were performed in a 96-well MultiScreen 0.45µm filtration plates (Millipore, U.K.). Each assay contained ~50pM [<sup>125</sup>I]IL-8 and membranes (equivalent to ~200,000 cells) in assay buffer [Tyrode's salt solution supplemented with 10mM HEPES (pH 7.4), 1.8mM CaCl<sub>2</sub>, 1mM MgCl<sub>2</sub>, 0.125mg/ml bacitracin and 0.1%(w/v) gelatin]. In addition, a compound of formula (I) according to the Examples was pre-dissolved in DMSO and added to reach a final concentration of 1%(v/v) DMSO. The assay was initiated with the addition of membranes and after 1.5 hours at room temperature the membranes were harvested by filtration using a Millipore MultiScreen vacuum manifold and washed twice with assay buffer (without bacitracin). The backing plate was removed from the MultiScreen plate assembly, the filters dried at room temperature, punched out and then counted on a Cobra γ-counter.

The compounds of formula (I) according to the Examples were found to have IC<sub>50</sub> values of less than (<) 10µM.

#### **Intracellular Calcium Mobilisation Assay**

Human neutrophils were prepared from EDTA-treated peripheral blood, as previously described (Baly *et al.* (1997) *Methods in Enzymology* 287 pp70-72), in storage buffer [Tyrode's salt solution (137mM NaCl, 2.7mM KCl, 0.4mM NaH<sub>2</sub>PO<sub>4</sub>) supplemented with 5.7mM glucose and 10mM HEPES (pH 7.4)].

The chemokine GROα (human, recombinant) was purchased from R&D Systems (Abingdon, U.K.). All other chemicals were of analytical grade. Changes in intracellular free calcium were measured fluorometrically by loading neutrophils with the calcium sensitive fluorescent dye, fluo-3, as described previously (Merritt *et al.* (1990) *Biochem. J.* 269, pp513-519). Cells were loaded for 1 hour at 37°C in loading buffer (storage buffer with 0.1%(w/v) gelatin) containing 5µM fluo-3 AM ester, washed with loading buffer and then resuspended in Tyrode's salt solution supplemented with 5.7mM glucose, 0.1%(w/v) bovine serum albumin (BSA), 1.8mM CaCl<sub>2</sub> and 1mM MgCl<sub>2</sub>. The cells were pipetted into black walled, clear bottom, 96 well micro plates (Costar, Boston, U.S.A.) and centrifuged (200g, 5 minutes, room temperature).

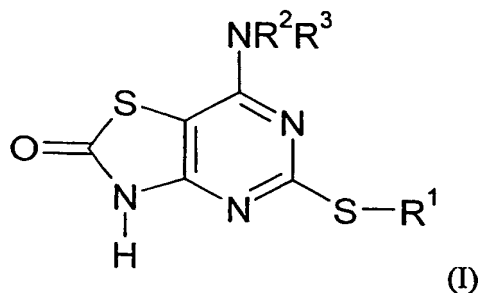
A compound of formula (I) according to the Examples was pre-dissolved in DMSO and added to a final concentration of 0.1%(v/v) DMSO. Assays were initiated by the addition of an A<sub>50</sub> concentration of GROα and the transient increase in fluo-3 fluorescence (λ<sub>Ex</sub>

=490nm and  $\lambda_{Em} = 520\text{nm}$ ) monitored using a FLIPR (Fluorometric Imaging Plate Reader, Molecular Devices, Sunnyvale, U.S.A.).

The compounds of formula (I) according to the Examples were tested and found to be  
5 antagonists of the CXCR2 receptor in human neutrophils.

## CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof:



in which

$R^1$  represents a  $C_3$ - $C_7$  carbocyclic,  $C_1$ - $C_8$  alkyl,  $C_2$ - $C_6$  alkenyl or  $C_2$ - $C_6$  alkynyl group, each of the groups being optionally substituted by one or more substituent groups independently selected from halogen atoms,  $-OR^4$ ,  $-NR^5R^6$ ,  $-CONR^5R^6$ ,  $-COOR^7$ ,  $-NR^8COR^9$ ,  $-SR^{10}$ ,  $-SO_2R^{10}$ ,  $-SO_2NR^5R^6$ ,  $-NR^8SO_2R^9$  or an aryl or heteroaryl group, both of which may be optionally substituted by one or more substituents independently selected from halogen atoms, cyano, nitro,  $-OR^4$ ,  $-NR^5R^6$ ,  $-CONR^5R^6$ ,  $-COOR^7$ ,  $-NR^8COR^9$ ,  $-SR^{10}$ ,  $-SO_2R^{10}$ ,  $-SO_2NR^5R^6$ ,  $-NR^8SO_2R^9$ ,  $C_1$ - $C_6$  alkyl or trifluoromethyl groups;

$R^2$  and  $R^3$  each independently represent a hydrogen atom, or a  $C_3$ - $C_7$  carbocyclic,  $C_1$ - $C_8$  alkyl,  $C_2$ - $C_6$  alkenyl or  $C_2$ - $C_6$  alkynyl group, the latter four groups may be optionally substituted by one or more substituent groups independently selected from:

- (a) halogen atoms,  $-OR^4$ ,  $-NR^5R^6$ ,  $-CONR^5R^6$ ,  $-COOR^7$ ,  $-NR^8COR^9$ ,  $-SR^{10}$ ,  $-SO_2R^{10}$ ,  $-SO_2NR^5R^6$ ,  $-NR^8SO_2R^9$
- (b) a 3-8 membered ring optionally containing one or more atoms selected from O, S,  $NR^8$  and itself optionally substituted by  $C_1$ - $C_3$ -alkyl or halogen,
- (c) an aryl group or heteroaryl group each of which may be optionally substituted by one or more substituents independently selected from halogen atoms, cyano, nitro,  $-OR^4$ ,  $-NR^5R^6$ ,  $-CONR^5R^6$ ,  $-NR^8COR^9$ ,  $-SO_2NR^5R^6$ ,  $-NR^8SO_2R^9$ ,  $C_1$ - $C_6$  alkyl and trifluoromethyl groups;



R<sup>4</sup> represents hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl or a phenyl group the latter two of which may be optionally substituted by one or more substituent groups independently selected from halogen atoms, phenyl, -OR<sup>11</sup> and -NR<sup>12</sup>R<sup>13</sup>

5 R<sup>5</sup> and R<sup>6</sup> independently represent a hydrogen atom or a C<sub>1</sub>-C<sub>6</sub> alkyl or phenyl group the latter two of which may be optionally substituted by one or more substituent groups independently selected from halogen atoms, phenyl, -OR<sup>14</sup> and -NR<sup>15</sup>R<sup>16</sup>, -CONR<sup>15</sup>R<sup>16</sup>, -NR<sup>15</sup>COR<sup>16</sup>, -SONR<sup>15</sup>R<sup>16</sup>, NR<sup>15</sup>SO<sub>2</sub>R<sup>16</sup>

or

10 R<sup>5</sup> and R<sup>6</sup> together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring system optionally containing a further heteroatom selected from oxygen and nitrogen atoms, which ring system may be optionally substituted by one or more substituent groups independently selected from phenyl, -OR<sup>14</sup>, -COOR<sup>14</sup>, -NR<sup>15</sup>R<sup>16</sup>, -CONR<sup>15</sup>R<sup>16</sup>, -NR<sup>15</sup>COR<sup>16</sup>, -SONR<sup>15</sup>R<sup>16</sup>, NR<sup>15</sup>SO<sub>2</sub>R<sup>16</sup> or C<sub>1</sub>-C<sub>6</sub> alkyl, itself  
 15 optionally substituted by one or more substituents independently selected from halogen atoms and -NR<sup>15</sup>R<sup>16</sup> and -OR<sup>17</sup> groups;

R<sup>10</sup> represents a hydrogen atom or a C<sub>1</sub>-C<sub>6</sub>-alkyl or a phenyl group, the latter two of which may be optionally substituted by one or more substituent groups independently selected  
 20 from halogen atoms, phenyl, -OR<sup>17</sup> and -NR<sup>15</sup>R<sup>16</sup>; and

each of R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup> independently represents a hydrogen atom or a C<sub>1</sub>-C<sub>6</sub>, alkyl, or a phenyl group.

25 2. A compound according to claim 1, wherein R<sup>1</sup> represents an optionally substituted benzyl group.

3. A compound according to claim 1 or claim 2, wherein one of R<sup>2</sup> and R<sup>3</sup> is hydrogen and the other is C<sub>1</sub>-C<sub>8</sub> alkyl substituted by hydroxy and one or more methyl or ethyl  
 30 groups.

4. A compound according to claim 1 selected from:

7-[(2-Hydroxy-1,1-dimethylethyl)amino]-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

(*R*)-7-[[1-(Hydroxymethyl)propyl]amino]-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

(*R*)-7-[(2-Hydroxy-1-methylethyl)amino]-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

5 5-[[2,3-Difluorophenyl)methyl]thio]-7-[(2-hydroxy-1,1-dimethylethyl)amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

5-[[2,3-Difluorophenyl)methyl]thio]-7-[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

10 5-[[2,3-difluorophenyl)methyl]thio]-7-[[2-(hydroxyethoxy)ethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

5-[[2,3-difluorophenyl)methyl]thio]-7-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

7-[(2-aminoethyl)amino]-5-[[2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

15 5-[[2,3-difluorophenyl)methyl]thio]-7-[(2-hydroxyethyl)amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

*N*-[2-[[5-[[2,3-difluorophenyl)methyl]thio]-2,3-dihydro-2-oxothiazolo[4,5-*d*]pyrimidin-7-yl]amino]ethyl]methanesulfonamide,

20 (+/-)-5-[[2,3-difluorophenyl)methyl]thio]-7-[[2-(2-hydroxyethoxy)-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

7-[[1*R*)-2-amino-1-methylethyl]amino]-5-[[2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

5-[[2,3-difluorophenyl)methyl]thio]-7-[[1*R*)-2-[(2-hydroxyethyl)amino]-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

25 5-[[2,3-difluorophenyl)methyl]thio]-7-[[1*R*)-2-(dimethylamino)-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

5-[[[4-(2-aminoethoxy)-3-chlorophenyl]methyl]thio]-7-[[1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

30 5-[[3-Chloro-4-methoxyphenyl)methyl]thio]-7-[[1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

- 5-[[3-Chloro-2-fluorophenyl)methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
- 5-[[[(2,3-Difluorophenyl)methyl]thio]-7-[[[(3*R*,4*R*)-4-hydroxypyrrolidin-3-yl]amino]-thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
- 5 5-[[[(2,3-Difluorophenyl)methyl]thio]-7-[(3*R*)-pyrrolidin-3-ylamino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
- 7-[[[(1*R*)-2-Hydroxy-1-methylethyl]amino]-5-[[[(2-methyl-4-thiazolyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
- 7-[[2-Hydroxy-1-(hydroxymethyl)ethyl]amino]-5-[[[(2-methyl-4-thiazolyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
- 10 thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
- 7-[(2-Hydroxy-1,1-dimethylethyl)amino]-5-[[[(2-methyl-4-thiazolyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
- 7-[(2-Hydroxy-1,1-dimethylethyl)amino]-5-[[[(2-methylphenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
- 15 5-[(2-Furanylmethyl)thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
- 7-[[[(1*R*)-2-Amino-1-methylethyl]amino]-5-[[[(3-chloro-2-fluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one
- (2*S*)-2-[[5-[[[(2,3-Difluorophenyl)methyl]thio]-2,3-dihydro-2-oxothiazolo[4,5-*d*]pyrimidin-7-yl]amino]-3-hydroxy-propanamide,
- 20 7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]-5-[(2-thienylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
- 7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]-5-[[[3-methyl-4-(methylsulfonyl)phenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
- 25 5-[[[3-chloro-4-(trifluoromethoxy)phenyl)methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
- 5-[[[2-fluoro-3-(trifluoromethyl)phenyl)methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
- 5-[[[(2,3-difluorophenyl)methyl]thio]-7-[2-[(dimethylamino)ethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
- 30

5-[[[(2-fluorophenyl)methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]-5-[[[(2-methoxyphenyl)methyl]thio] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

5 7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]-5-[(2-phenoxyethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]-5-[[[(3-methylphenyl)methyl]thio] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

10 5-[[[(2-fluoro-3-methylphenyl)methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

5-[[[(3-chlorophenyl)methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

5-[[[(3-bromophenyl)methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

15 5-[[[4-(difluoromethoxy)phenyl]methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

(+/-)-5-[[[(2,3-difluorophenyl)methyl]thio]-7-[[2-hydroxy-1-(methoxymethyl)ethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

20 7-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

5-[[[(2-bromophenyl)methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

5-[[[(2,3-Difluorophenyl)methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

25 5-[[[3-Chloro-2-fluorophenyl)methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

(+/-)-5-[[[(2,3-difluorophenyl)methyl]thio]-7-[[2-hydroxy-1-(methoxymethyl)ethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

30 7-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

7-[[*(1R)*-2-Hydroxy-1-methylethyl]amino]-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

5-[(5-chloro-1,2,3-thiadiazol-4-yl)thio]-7-[[*(1R)*-2-hydroxy-1-methylethyl]amino]-thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

5 and their pharmaceutically acceptable salts and solvates.

5. A compound according to claim 1 selected from:

5-[[*(2,3*-Difluorophenyl)methyl]thio]-7-[[*(1R)*-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one sodium salt,

10 5-[[*(3*-Chloro-2-fluorophenyl)methyl]thio]-7-[[*(1R)*-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one sodium salt,

(+/-)-5-[[*(2,3*-difluorophenyl)methyl]thio]-7-[[2-hydroxy-1-(methoxymethyl)ethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one sodium salt,  
7-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one sodium salt, or

15 7-[[*(1R)*-2-Hydroxy-1-methylethyl]amino]-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one sodium salt.

6. A compound according to claim 1 selected from:

20 7-[[*(1R)*-2-amino-1-methylethyl]amino]-5-[[*(2,3*-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one trifluoroacetate,

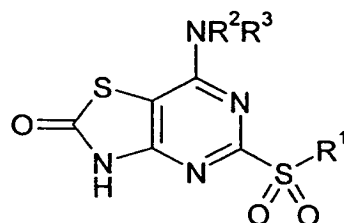
5-[[*(2,3*-difluorophenyl)methyl]thio]-7-[[*(1R)*-2-[(2-hydroxyethyl)amino]-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one trifluoroacetate,

5-[[*(2,3*-difluorophenyl)methyl]thio]-7-[[*(1R)*-2-(dimethylamino)-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,  
25 5-[[[4-(2-aminoethoxy)-3-chlorophenyl]methyl]thio]-7-[[*(1R)*-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one trifluoroacetate,  
5-[[*(2,3*-difluorophenyl)methyl]thio]-7-[2-[(dimethylamino)ethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one monohydrochloride, or

30 5-[[*(2,3*-Difluorophenyl)methyl]thio]-7-[(3*R*)-pyrrolidin-3-ylamino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one dihydrochloride.

7. A process for the preparation of a compound of formula (I) as defined in claim 1 which comprises:

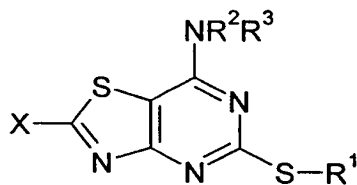
(a) treating a compound of formula (IIA):



(IIA)

where R¹, R² and R³ are as defined in formula (I) with a thiol R¹SH in the presence of a suitable base, or

(b) treatment of a compound of formula (IIB):

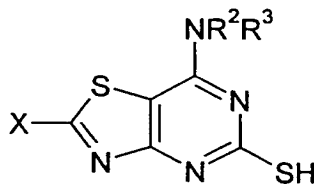


(IIB)

where R¹, R² and R³ are as defined in formula (I) and X is a leaving group with a metal alkoxide, followed by treatment with an acid or base, and optionally after (a) or (b) forming a pharmaceutically acceptable salt.

8. A compound of formula (IIA) or (IIB) as defined in claim 7.

9. A compound of formula (IIIA):



(IIIA)

where  $R^2$  and  $R^3$  are as defined in formula (I) and X is  $NH_2$ ,

10. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 6  
5 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.
11. A process for the preparation of a pharmaceutical composition as claimed in claim 10 which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 6 with a pharmaceutically  
10 acceptable adjuvant, diluent or carrier.
12. A compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as claimed in any one of claims 1 to 6 for use in therapy.
- 15 13. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 6 in the manufacture of a medicament for use in therapy.
- 20 14. A method of treating a chemokine mediated disease wherein the chemokine binds to one or more chemokine receptors, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 6.
- 25 15. A method according to claim 14 in which the chemokine receptor belongs to the CXC chemokine receptor subfamily.
16. A method according to claim 14 or 15 in which the chemokine receptor is the CXCR2 receptor.
- 30 17. A method of treating an inflammatory disease in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 6.
- 35 18. A method according to claim 17, wherein the disease is psoriasis, a disease in which angiogenesis is associated with raised CXCR2 chemokine levels, or COPD.

19. A method according to claim 15, wherein the disease is psoriasis.



# INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 00/03692

## A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 513/04, A61K 31/519, A61P 17/06, A61P 29/00 // (C07D 513/04, 277:00, 239:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 0009511 A1 (ASTRA PHARMACEUTICALS LTD.), 24 February 2000 (24.02.00), page 78, line 16 - line 19; page 79, line 15 - line 16; the examples; the claims	8
P,A	--	1-7,9-19
P,A	WO 9951608 A1 (DU PONT PHARMACEUTICALS COMPANY), 14 October 1999 (14.10.99)	1-19
A	WO 9808847 A1 (PFIZER INC.), 5 March 1998 (05.03.98), page 6, formula I-K, claims 1, 16-19	1-19
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☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

Date of mailing of the international search report

16 January 2001

23.02.01

Name and mailing address of the International Searching Authority  
European Patent Office P.B. 5818 Patentlaan 2  
NL-2280 HV Rijswijk  
Tel(+31-70)340-2040, Tx 31 651 epo nl,  
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Authorized officer

GERD STRANDELL/EÖ  
Telephone No.

—2—  
**INTERNATIONAL SEARCH REPORT**

International application No.  
**PCT/GB 00/03692**

**C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0778277 A1 (PFIZER INC.), 11 June 1997 (11.06.97), the claims  -- -----	1-19

# INTERNATIONAL SEARCH REPORT

International application No.  
**PCT/GB00/03692**

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **14-19**  
because they relate to subject matter not required to be searched by this Authority, namely:  
**see next sheet**
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.  
PCT/GB00/03692

Claims 14-19 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

27/12/00

International application No.

PCT/GB 00/03692

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
WO	0009511	A1	24/02/00	AU	5662599 A	06/03/00
				SE	9802729 D	00/00/00
WO	9951608	A1	14/10/99	AU	3213699 A	25/10/99
				EP	0959418 A	24/11/99
				US	6107294 A	22/08/00
WO	9808847	A1	05/03/98	AP	762 A	13/09/99
				AP	9701077 D	00/00/00
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				BG	103189 A	30/09/99
				BR	9711970 A	24/08/99
				CN	1227554 A	01/09/99
				CZ	9900681 A	17/11/99
				EP	0923582 A	23/06/99
				HR	970454 A	31/08/98
				HU	9903965 A	28/03/00
				IL	127566 D	00/00/00
				JP	2000502723 T	07/03/00
				NO	990927 A	26/02/99
				PL	332040 A	16/08/99
				ZA	9707687 A	01/03/99
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				JP	9188682 A	22/07/97
				JP	2000109431 A	18/04/00

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